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Pre and post characterization of ODTs with emphasis on compression force and quality of super-disintegrants: *In vivo* analysis in healthy volunteers

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Abstract: Oral dispersible tablets (ODTs) are patient compliant dosage forms which rapidly disintegrate in the mouth following active absorption with rapid onset of action. The current study was designed to resolve compression problems used for ODTs, as high compression force exhibited hardness and drug release problems. Formulations, F1-F9 were compressed at three different forces 44, 54, and 64 kN using cross-carmellose sodium (CCS) and sodium starch glycolate (SSG) and evaluated for pre and post compression. Formulations F1, F4 and F7 which were compressed at 44 kN showed hardness ranges between 5.09-6.15 with lowest DT (less than 15 s) and better LTZ release. While F2, F5 and F8 (compressed at 54 kN) demonstrated hardness in between 6.90-7.02. Similarly, F3, F6 and F9 compressed at 64 kN showed hardness values between 8.70-8.98 with increased DT and slow LTZ release. Friability results for all the formulations were within United States Pharmacopeial (USP) specifications (<1%). All formulations depicted t-test value <0.5, hence it found that all formulations showed significant statistical value within limits, however best compression force 44 kN showed low p value. It was concluded that optimized compression force for ODTs was 44 kN among all employed forces that exhibited desirable drug release.

Keywords: Oral dispersible tablet, volunteers study, levocetirizine hydrochloride, compression force, super-disintegrant.

INTRODUCTION

The oral disintegrating tablets (ODTs) is a scalable technique that is designed to release the drug in oral or buccal cavity to be absorbed below the sub-lingual region. Geriatric, pediatric and some adults, which constitute a reasonable presentation of world's population, have clinical complaint regarding difficult swallowing (Hanning *et al.*, 2016). Drug delivery to this unique subset of patients can be facilitated by oral dispersible tablets (Chinwala, 2020). Some of the significant benefits of ODTs include instant disintegration of tablet as well as absorption of drug in mouth pharynx and esophagus prior to the stomach, thereby bypassing first pass effect and increased bioavailability, reducing dosage and improving clinical efficacy. ODTs can rapidly treat conditions that require immediate treatment, such as motion sickness, an allergic reaction to a foreign matter, or coughing. These ODTs enhances patient compliance by lowering the possibility of clogging up or suffocation that transpire due to physical obstruction (Al-Husban *et al.*, 2010). Moreover, ODTs have an exemplary characteristic of withholding long term stability and sustainability as a solid dosage form and advanced bioavailability. However, some problems are associated with the large scale manufacturing of ODTs which might include, but not limited to the poor friability and hardness of the tablets (Hindija *et al.*, 2021). Researchers and large scale manufacturers have utilized direct compression, dry and wet granulation as method of formulation of the dosage form, yet direct compression is one of the most cost-effective technique regarding the formulation of ODTs. Time of production, steps involved, low labor and economic effectivity are some of the common advantages over granulation method (Al-Khattawi and Mohammed, 2013). However, the better flow characteristics of the ingredients used in ODTs compression is a critical requirement of adopting direct compression methodology (Kokott *et al.*, 2021).

Levocetirizine (LTZ) is an anti-inflammatory, non-sedating, specific histamine H_1 receptor antagonist which belongs to third generation, having potential angiogenic activity. LTZ prevents the side effects of endogenous histamine by binding with peripheral H_1 receptor present on effector cell surfaces. It exhibits rapid absorption, and effective plasma concentration is achieved with in 3 h after dosing and eliminated in urine in unaltered form

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(Strolin Benedetti *et al.*, 2001). Although attempts have been made previously, regarding the formulation of LTZ to evaluate the efficacy of the drug through buccal route to achieve early maximum drug concentration (Ino *et al.*, 2020). However, ODTs typically presents compressibility issues, when it is tabulated at low hardness pressure in order to comply with the drug release compendial specifications (Al-Khattawi and Mohammed, 2014). Hence, the current study employed 2 levels of variables factors i.e. compressibility force and quality of super-disintegrant in order to overcome hardness and friability issues related to compressibility of the orodispersible tablets.

MATERIALS AND METHODS

Materials

The anti-histaminic drug was sourced from Titlis® Pharma (Pakistan). The polymer sodium starch glycolate (SSG) was purchased from Yung Zip Chemical Ind®, and cross-carmellose sodium (CCS) were purchased from Mingtai Chemical® (Taiwan). Similarly, Aerosil® (Cabot®), microcrystalline cellulose (MCC), and dicalcium phosphate dihydrate were purchased from JRS Pharma® (Germany). Magnesium Stearate was purchased from Peter Ge® (Malaysia). Menthol was purchased from Anhui Great Oils® (China).

Study design

Nine formulations were designed by using varied concentration of two super-disintegrants i.e. CCS and SSG by employing three variable compression forces (CF) according to table 1. The concentrations of LTZ and excipients were kept same in formulations F1, F2, and F3 by adding 6.25 and 5 mg of SSG and CCS respectively (Vlad *et al.*, 2021), but compressed at different CF of 44, 54 and 64 kN respectively. Similarly, the formulations F4, F5, and F6 were also compressed at different CF by adding 4 and 7.25 mg of CCS and SSG respectively. The concentrations of CCS and SSG were 6 and 5.25 mg in formulations F7, F8 and F9 and compressed at 44, 54, 64 kN respectively by using ZP-35 rotary tablet machine with 6.5 mm bisect line faced punch. Total weight of tablet was kept 130 mg.

Pre-formulation studies

Pre-formulations studies were performed for analytical and pharmaceutical investigations that was executed preceding the formulation development of LTZ.

Angle of repose (AR)

The funnel method, also known as the piling method, is the most commonly used experimental technique in which material falls from a specified height onto a flat plate. The prepared formulation was transferred to a funnel that was held vertically to a smooth surface at a height of 2 cm in this experiment. A cotton plug was used to block the funnel's tip. Maximum height was obtained by allowing free flow of powder from the funnel. Keep the funnel tip close to the growing cone and gradually raise it as the pile grows to reduce the impact of falling particles. AR was calculated according to Equation 1.

$$\theta = \tan^{-1}\left(\frac{2h}{d}\right) \quad \text{Eq. 1}$$

Where, θ =angle of repose, h= height of heap of powder and d is the diametric length of the heap (Ahmed *et al.*, 2021).

Bulk density (BD)

For calculating bulk density, the dispersed powder was allowed to settle in the container under the effect of gravity. In this experiment, the sample powder was precisely measured (M) and the entire sample was filtered through sieve no. 18 (USP). This powder mixture then shifted into a graduated cylinder of 100 mL and the unsettled loose powder volume (V_b) was calculated (Eq. 2) (Yasmin *et al.*, 2020).

$$\text{BD} = \frac{M}{Vb} \quad \text{Eq. 2}$$

Tapped density (TD)

The tapped density was calculated by tapping of aerated powder sample within the container. The initial volume was measured by transferring sample powder blend in measuring cylinder. The cylinder was then tapped 100 times on a plane hard wooden surface to obtain the powder's constant volume (V_a). When friction between particles is reduced, the particles rearrange, resulting in practical and advanced packing conditions (Marzouk *et al.*, 2021).

$$\text{TD} = \frac{M}{Va} \quad \text{Eq. 3}$$

Compressibility index (CI)

Carr's index of powder blend of each formulation was calculated to determine percent compressibility (Al-Akayleh *et al.*, 2020).

$$\text{Cl} = \frac{TD - BD}{TD} \quad \text{Eq. 4}$$

Hausner's ratio (HR)

The flow and compressibility of the powder blend can be demonstrated by the ratio of tapped density to bulk density. Hausner's ratio measures the cohesiveness of powder. The higher the ratio of tapped density to bulk density, the greater the cohesion (Bowles *et al.*, 2018).

$$\text{HR} = \frac{TD}{BD} \quad \text{Eq. 5}$$

(Fourier transform infrared spectroscopy) FTIR study

It was performed to ensure that the active drug was compatible with the other formulation additives. Individual excipients used in the current study were also analyzed using FTIR at a scanning range of 4000-600

cm^{-1} after the spectrum of active drugs was recorded (Sheeba & Chaudhary, 2020). The change in vibrational or stretching bands of key functional groups in FTIR spectrum was used as the indication of drug-excipient interactions. The pellet was prepared by potassium bromide pressed pellet technique. The developed pellet was retained in the IR chamber, and by using opus software of Bruker FTIR spectrophotometer the IR spectra of the mixtures were recorded.

Post compression evaluative parameters

Physical appearance

The shape and size of uncoated tablets, whether oval, round, or caplets, ranging from 150-900 mg, were carefully examined. Color preference was determined by exposing the tablets to both natural and artificial light. Dimensions and the gloss finish were also determined (Irfan *et al.*, 2016).

Weight variation

The weight variation test was carried out by weighing 20 tablets, thereafter calculating average weights, and comparing the individual tablet weights to the average, according to the USP (Javed *et al.*, 2022). Content uniformity of tablet was carried on n = 20 tablets, selected randomly and individually weighed on a Sartorius® balance (Model CP225D, Bradford, MA, USA). Once average weight was attained, the standard deviation was calculated from the mean value using Equation 6.

$$\mathrm{SD} = \frac{W_a - W_i}{W_a} \times 100 \qquad \text{Eq. 6}$$

Hardness, thickness and diameter

The thickness of every tablet (n = 20 tablets) was measured with the help of digital vernier caliper (Digital Caliper Workzone®, UK). Hardness test is a force needed to break the tablet in diametric compression test. Three randomly selected tablets were adjusted in vertical position between arms of tester and values denoted by screen of tester in millimeter units were noted. Average of three readings was used for calculating standard deviation. Digital hardness tester was used for calculation (Manda *et al.*, 2018). Thickness and diameter variation is governed by the amount of different polymers added and force of punching employed in compression. Vernier Caliper was used to assess the thickness and diameter of the formulated tablets (Razzaq *et al.*, 2021). Simply tablet was placed between the jaws and slide the scale jaw to press the tablet against the stationary jaw to measure the thickness. The value on the display screen is recorded, and it depicts the actual thickness of tablet (Tashan *et al.*, 2020).

Friability

Friability testing is used to determine tablet durability during packing and transportation. The testing of tablet friability entails weighing randomly selected ten tablets and then transferring them in rotating drum of friabilator. Then 100 revolutions were completed by adjusting 25 revolutions per minute for 4 min. The sample was then reweighed to calculate the weight loss percentage (Muhammad *et al.*, 2022). Then tablets were dedusted and weigh again to calculate percentage friability by Equation 7.

$$\text{Friability}\,\% = \frac{W_i - Wf}{W_i} \times 100 \qquad \text{Eq. 7}$$

Wetting time (Wt) and water absorption ratio (R)

Briefly, whatman filter paper, folded once diametrically, was kept in a petri dish of 8.5 cm diameter. A small amount of water (8 mL) containing the water soluble dye Rhodamine B (0.1 g) was poured to the filter paper adjusted in petri dish. At t=0, the tablet was precisely placed on the filter paper and complete wetting time was recorded. The emergence of dye on tablet surface is the indication of complete wetting. Following completion, the wetting tablet was reweighed (W_a) and R was calculated (Eq. 8) (Akdag *et al.*, 2020).

$$\mathrm{R} = \frac{W_a - W_b}{W_b} \times 100 \qquad \text{Eq. 8}$$

The water absorption ratio is represented by *R* in the above equation, whereas weight of tablets before and after water absorption is represented by W_b and W_a respectively.

In vitro disintegration

The *in vitro* disintegration analysis was performed by using deionized water kept at 37 °C on a calibrated Pharmatest® PTZ Auto, PTFE Disintegration tester (PharmaTest, Germany). The pH of the deionized water was adjusted to 6.8 to mimic simulations of salivary fluid. The test was performed four times with four ODTs and the average DT standard deviation was calculated (Soulairol *et al.*, 2018).

In vivo tablet disintegration and adaptability response

The tablet disintegration time in the oral cavity was assessed on six healthy volunteers. Before the start of the experiment, favorable opinion regarding the conductance of evaluation test was obtained from the Institutional research Ethics Committee (REC/DPP/FOP/6C). The study protocols were in accordance with the principles of the Declaration of Helsinki. After rinsing the mouth with purified water, the tablet was held in the mouth of volunteers without chewing until the tablet disintegrate completely. The time required for complete disintegration in the oral cavity was recorded (Amelian *et al.*, 2017). However, LTZ was not added for the evaluation of the *in vivo* time and the evaluation was performed without the addition of drug.

Dissolution test

A USP dissolution apparatus type II was used to determine the release profiles of LTZ from the formulated

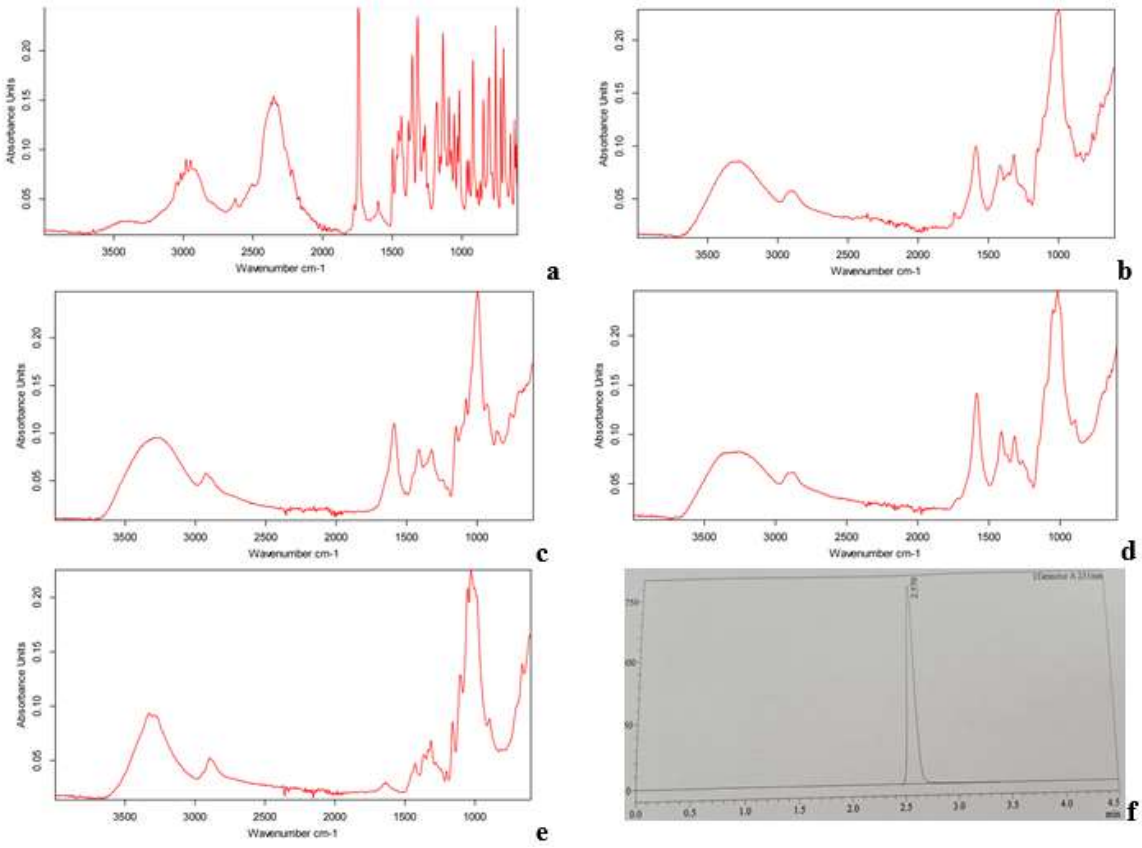

Fig. 1: FTIR spectrum of a. LTZ, b. physical mixture, c. SSG, d. CCS, e. MCC and f. HPLC chromatogram depicting the peak of LTZ using the devised method.

ODTs. Briefly, the formulations were suspended in 750 mL of phosphate buffer (pH 6.8) and stirred at 75 rpm at 37±1 °C. However, the sink conditions were maintained during the dissolution test. At predetermined time intervals, samples were withdrawn from the dissolution vessel while fresh dissolution medium was added to replenish dissolution volume.

For sample preparation 20 tablets were weighted and powdered then powder equivalent to 10 mg of LTZ was taken into 100 mL volumetric flask dilute to volume with mobile phase. It was sonicated for 15 min and kept on stirring for 15 min and make volume up to mark using the mobile phase as follows.

HPLC instrumental settings

An HPLC method was used to determine the percentage drug release at wavelength of 231 nm. Briefly, the analysis was performed using Shimadzu® (model CTO 20A) machine equipped with C_{18} Agilent (4.6 mm x 25 cm, 5µm) column with auto sampler injector used at 10µL sample capacity. The peak of LTZ was obtained at 2.57 min following analytical injection. For preparation of mobile phase 350 mL of 0.02 M disodium hydrogen phosphate was mixed with 650 mL acetonitrile (adjust to pH 7.0 with phosphoric acid). Then the mixture was filtered and degassed. For preparation of standard solution, 10mg of LTZ was transfer to a 100 mL volumetric flask and dilute to volume with mobile phase. The solution was passed across a membrane filter of 0.45 µm pore size.

Moisture absorption study

These studies were done by placing the selected three tablets from each formulation into a calcium chloride containing desiccator at 37 °C. For 75% humidity, saturated solution of sodium chloride was placed in the bottom of desiccator. Tablets were initially weighed and then after 24 h again weighed to calculated moisture gain (Ghourichay *et al.*, 2021).

Stability study

These studies were conducted according to ICH (International Council of Harmonization) guidelines. Tablets from each formulation were stored under extreme condition that is 45 °C temperature and 75% Relative Humidity. The duration of the study was 30 days. Tablets were checked after 15 days and finally after 30 days for friability, hardness, disintegration and drug release (Spandana *et al.*, 2020).

Table 1: Composition of formulations of LTZ with varied compression force

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
SSG (mg)	6.25	6.25	6.25	7.25	7.25	7.25	5.25	5.25	5.25
CCS (mg)	5	5	5	4	4	4	6	6	6
CF (kN)	44	54	64	44	54	64	44	54	64

Table 2: Pre-formulation evaluation parameters

Code	BD (g/mL)	TD (g/mL)	CI (%)	HR	AR (°)
F1-F3	0.653 ± 0.013	0.726 ± 0.017	10 ± 0.5	1.11 ± 0.006	24.17 ± 1.01
F4-F6	0.668 ± 0.007	0.760 ± 0.004	12.11 ± 1.04	1.14 ± 0.018	22.09 ± 2.01
F7-F9	0.687 ± 0.005	0.801 ± 0.007	14.24 ± 0.6	1.17 ± 0.009	26.93 ± 0.32

Table 3: Physical characterization of the formulated ODTs

Code	Average Weight (mg ± SD)	Hardness (Kg/cm^2 ± SD)	Thickness (mm ± SD)	Diameter (mm ± SD)	Friability (%)
F1	131 ± 4.05	5.09 ± 0.51	3.65 ± 0.05	6.53 ± 0.03	0.45
F2	130 ± 3.17	6.99 ± 0.14	3.45 ± 0.01	6.50 ± 0.07	0.34
F3	131 ± 2.99	8.70 ± 0.34	3.29 ± 0.06	6.54 ± 0.05	0.23
F4	129 ± 3.68	5.72 ± 0.20	3.70 ± 0.09	6.51 ± 0.02	0.48
F5	129 ± 1.97	6.90 ± 0.15	3.39 ± 0.03	6.52 ± 0.09	0.41
F6	130 ± 2.81	8.92 ± 0.15	3.25 ± 0.07	6.57 ± 0.04	0.19
F7	133 ± 4.29	6.15 ± 0.10	3.59 ± 0.04	6.53 ± 0.06	0.53
F8	132 ± 3.56	7.02 ± 0.09	3.34 ± 0.02	6.51 ± 0.05	0.32
F9	133 ± 1.84	8.98 ± 0.05	3.17 ± 0.08	6.52 ± 0.08	0.21

STATISTICAL ANALYSIS

The student t test (statistical analysis) was performed using SPSS v.22 whereas the values of standard deviation of the physical parameters were calculated from Microsoft Excel 2013.

RESULTS

FTIR

Spectrum of pure LTZ, which has characteristic bands at 2980.45 cm^{-1} due to aliphatic and aromatic C-H stretching vibrations, also exhibited strong absorption band at 2353.49 cm^{-1} (fig. 1a) owing to the presence of carboxylic acid OH stretching vibration (Watson, 2020). The C = O stretching vibrations at 1742.53 cm^{-1} and at 1433.20 cm^{-1} represented the stretching vibration of phenyl nucleus skeletal (Al-Kubati *et al.*, 2022). In addition, the absorption bands were at 1354.78 cm^{-1} and 1317.74 cm^{-1} due to vibrational stretching of C-N and C-O respectively (Akhtar *et al.*, 2020). When these peaks were correlated with mixture of pure drug LTZ and excipients (fig. 1b), the stretching vibrations were almost similar as the mixture sample showed C-H stretching vibrations at 3266.62 cm^{-1} and C = O stretching vibration at 1588.26 cm^{-1}. The phenyl nucleus skeletal of the mixture was characterized by stretching vibration at 1318.03 cm^{-1}. The major excipient SSG showed C-H stretching at 3303.26 cm^{-1} (fig. 1c) and C = O starching at 1588.66 cm^{-1}, while the peaks at 3285.01 and 3326.30 cm^{-1} represented C-H of CCS and MCC respectively (fig. 1d and fig. 1e). Similarly, the C = O stretching vibrations of these two excipients were shown at 1566.42 and 1028.48 cm^{-1}, respectively.

Pre-formulation characterization

All the 9 formulations of oral dispersible tablets (ODTs) were prepared by using the drug model LTZ. Two different types of super-disintegrant were used by employing different range of compression forces to check the effect of these forces on release profile of drug. To assess the rheological characteristics of the drugs, powder samples were evaluated for different parameters before compression. The values of bulk density and tapped density vary from 0.71 to 0.81g/mL respectively. No considerable difference was found in these values. The values of bulk and tapped densities were further utilized for evaluating Hausner's Ratio (HR), Compressibility Index (CI) and Angle Ratio (AR).

Physical characterization

The percentage deviation of weight remained within the allowed limits and hence weight variation test was within the Specified USP limits. The thickness of all the tablets was confirmed to be within the range of 3.17-3.7 0mm, and the diameter ranges from 6.50-6.57 mm. Hence, different compression forces were used for each formulation, the results demonstrated different hardness

Table 4: Result of physicochemical evaluation parameters

Formulation code	*In vitro* DT (s ± SD)	*In vivo* DT (s)	Wetting time (s ± SD)	Water absorption ratio	Moisture gain (ratio ± SD)	*In vivo* adaptability response
F1	10 ± 0.28	11	11 ± 0.24	46.29 ± 1.49	1.04 ± 0.06	palatable
F2	17 ± 0.95	18	18 ± 0.92	78.33 ± 1.06	1.84 ± 0.07	palatable
F3	21 ± 0.73	21	24 ± 0.76	86.36 ± 1.18	2.67 ± 0.12	palatable
F4	12 ± 0.74	13	13 ± 0.49	58.33 ± 1.13	1.13 ± 0.04	palatable
F5	19 ± 0.38	20	20 ± 0.47	81.23 ± 0.93	2.01 ± 0.07	palatable
F6	21 ± 0.98	20	26 ± 0.05	90.17 ± 0.15	2.72 ± 0.16	palatable
F7	13 ± 0.59	14	15 ± 0.59	64.81 ± 1.17	1.13 ± 0.02	palatable
F8	20 ± 0.41	19	21 ± 0.31	87.51 ± 1.21	2.07 ± 0.01	palatable
F9	24 ± 0.16	23	27 ± 0.21	93.66 ± 1.53	2.79 ± 0.09	palatable

Table 5: Outcomes of LTZ release from the ODTs formulations as function of mean drug release ± standard deviation

Time min	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	32.1±1.23	24.2±2.68	21.96±1.97	30.6±3.01	23.1±2.21	21.6±1.79	30.6±1.88	22.6±2.69	20.9±2.44
3	64.9±2.51	48.9±1.37	42.49±2.01	63.3±1.19	46.3±1.34	41.5±2.29	62.8±2.94	44.4±2.21	40.8±1.62
5	97.2±0.37	72.6±0.51	63.76±0.26	96.2±0.49	70.8±0.51	62.1±0.38	94.9±0.46	68.2±0.51	61.1±0.28

Table 6: Stability Studies of selected formulation

Days	Code	Hardness (Kg/cm^2)	Friability (%)	DT (s)	LTZ release (%)
15 days	F1	5.02	0.45	10	97.12
	F4	5.15	0.48	12	96.17
	F7	4.87	0.56	13	94.87
30 days	F1	5.18	0.47	14	97.09
	F4	4.97	0.51	16	96.06
	F7	4.93	0.61	18	94.82

ranges. Formulations F1, F4 and F7, which were compressed at 44 kN, displayed hardness that ranges from 5.09-6.15. Formulations F2, F5, F8, that were compressed at 54 kN exhibited hardness that ranges from 6.90-7.02, whereas formulations F3, F6, F9, which were compressed at 64 kN, exhibited hardness that ranges from 8.70 - 8.98. These results represented that with the increase of compression force, hardness of tablet also increased, and therefore, this also effected release profile of drug (Ijitsu *et al.*, 2021). All formulations displayed less than 1% of friability value that ranges from 0.19-0.53, ultimately exceeding the official limits (Samvedna *et al.*, 2018).

Physicochemical characterization

Disintegration time is a critical parameter for evaluation of oral dispersible tablets since too poor disintegration may refrain the drug to be release from the dosage form. In present study, different compression forces were used, and wide range of hardness were observed that ultimately effected disintegration time of tablet. Formulations F1, F4, F7 compressed at 44 kN exhibited lowest disintegration time while F3, F6, F9 compressed at 64 kN exhibited highest range of disintegration time. The product was tested voluntarily and approximate results were confirmed between *in vitro* and *in vivo* DT (table 4). The taste was also palatable as sodium saccharin was used as a sweetening agent. The volunteers were apprehended to be a part of current study. Wetting time of formulations compressed at lowest compression force was less than those that were compressed at higher compression forces. The formulation F1 represented lowest wetting time of 11±0.24 s while F9 represented highest wetting time of 27±0.21 s (table 3). The water absorption ratio values results revealed that formulations F1, F4, F7 had lowest water absorption values 46.29-64.81 that indicated reduced swelling and water absorption capability of super-disintegrants in the designed dosage formulations.

Drug release

Results of this test clearly explained that formulations that were compressed at lower compression forces have exhibited best release profile as compared to those that were compressed at higher compression forces (table 5). Hence, the formulations F1, F4, F7 were considered to be high-grade oral dispersible formulations of LTZ that were compressed at 44 kN. The best amongst all selected formulations was Formulation F1 since it indicated lowest DT along with desirable release profile according to USP compendia (Puttewar *et al.*, 2010). The stability studies executed on selected formulations also reveals that DT and release profile of F1 formulation was least effected by the stressful storage conditions. Hence it was concluded that F1 is formulation with best super-disintegrants combination that fulfill all criteria of an ideal ODTs.

Stability study

Stability study of selected formulations F1, F4, F7 was carried out. The hardness of optimized formulation was not effected considerably even after 30 days. Parameters such as friability, and percentage release were also found to be within the USP Pharmacopeial limits (table 6).

DISCUSSION

Herein, the current study was aimed to deliver Levocetirizine (LTZ) with varied force of compression and quality of super-disintegrant. In precompression studies, values of bulk and tapped density were ranged between 0.71 to 0.81 g/mL respectively while angle of repose (AR) was in the range of 22.09 to 26.93º. For Hausnar's Ratio (HR) and Carr's Index (CI), it was calculated to be less than 1.25 and 20, respectively, indicating excellent flow.

The pre-compression evaluation illustrated the particle-particle interaction and free flowing properties of powder. All the values lie within official limits as the AR between 25-30, HR less than 1.25 and CI less than 20. All formulations exhibited excellent flow properties. Because of the same concentration of LTZ and additives, the pre-compression findings were identical for every three formulations i.e. F1 to F3, F4 to F6 and F7 to F9 (table 2). All the tablets were checked critically and found to be smooth, round biconvex having bisect line in one side of tablet. Similarly, friability and weight variation values were in accordance with USP specifications. Moisture gain study was performed for each formulation to estimate the ability to absorb moisture. It is important since the moisture presence may deteriorate the flow properties of the product (Asha *et al*., 2018).

The essential parameter of oral dispersible tablets (ODTs) was dissolution test which was in accordance with compendial specifications. The stability study performed on selected formulations was found to be in accordance with official stability study outcomes (Panhale *et al.*, 2021). It emphasizes that the formulation was found stable under tested conditions. For statistical analysis, the value of t-test did not exceed 0.05, which affirms that the formulations undergoing stability studies were unaffected in terms of parameters evaluated by the harsh conditions (Amelian *et al.*, 2017). The student paired t-test was applied on the prepared formulations to analyzed significant differences between the drug release and the stability conditions. Formulations F1, F4, F7 which were compressed at 44 kN have probability value of 0.0924, while other formulations F2, F5, F8 and F3, F6, F9 compressed at 55 and 64 kN, have probability values of 0.3273 and 0.1012 respectively. Conclusively, the formulations were stable at the end of stated time period. Formulations F1, F4, F7 which were compressed at 44 kN have p value of 0.0924, while other formulations F2, F5, F8 and F3, F6, F9 compressed at 55 and 64 kN respectively exhibited the values 0.327 and 0.101.

CONCLUSION

Current study was aimed to formulate ODTs of LTZ by using best super-disintegrant combination with optimum compression force that do not disturb DT and also have sufficient mechanical strength. It was concluded by FTIR spectra that the super-disintegrant used were highly compatible with pure drug LTZ, as no noticeable variations were seen in peaks of pure drug and mixture of excipients and drug. The designed formulations using varied concentration of super-disintegrant CCS and SSG showed satisfactory results of all pre-formulations and post-formulations parameters with little variations in values, but the most valuable results were found with lowest compression force used as it resulted in lowest DT which was the main objective of the study. The other issue of low mechanical strength was also resolved by varied concentration of excipients and the friability result were found in official limits. The selected formulations that showed lowest DT with sufficient mechanical strength along with best release profile were then subjected to stability study for one month under extreme conditions according to ICH guidelines. The stability studies results were also found in official limits and there were no noticeable changes in any parameter. Thus it was concluded that the optimized results can be achieved at lowest compression force by using SSG and CCS as super-disintegrant.

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