MS.ID-IJPBS-2304
International Journal of Pharmacy and Biological Sciences-IJPBS™ (2022) 12 (1): 83-89
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Pharmaceutical Sciences | OA Journal | MCI Approved | Index Copernicus

Formulation and Evaluation of Mouth Dissolving Tablets of Levocetirizine Dihydrochloride

Vijay Yadav[1*], Sharad Pudasaini[1], Pooja Shree Koirala[1], Lalita Laghu[1], Sarita Poudel[1], Sangita Kumari Sah[1], Rabindra Kumar Rokaya[2], Kedar Prasad Shah[3], Nabin Thapa Magar [4], Lalit Mohan Pant[1]

[1]Department of Pharmacy, Hope International College, Purbanchal University, Satdobato, Lalitpur, Nepal.
[2]Department of Pharmacy, Karnali Academy of Health Sciences, Jumla, Nepal.
[3]Department of Pharmacy, Kantipur Academy of Health Sciences, Purbanchal University, Kathmandu, Nepal.
[4]Department of Pharmacy, School of Health Sciences, Purbanchal University, Morang, Nepal.

Received: 12 Oct 2021 / Accepted: 6 Nov 2021/ Published online: 01 Jan 2022
*Corresponding Author Email: vijay.yadava456@gmail.com

Abstract

Background: Synthetic super disintegrants are used in the tablet formulation to improve the rate and extents of tablet disintegration thereby increasing the rate of drug dissolution. **Aim:** The purpose of the present study was to formulate levocetirizine orodispersible tablets using starch glycate and croscarmellose as super disintegrants to improve the onset of action, therapeutic efficacy, patient compliance and convenience. **Methodology:** Altogether eight formulations of Levocetirizine tablets were prepared by direct compression method. The powder blend was initially studied for pre-compression parameters and compressed tablets were evaluated for thickness, hardness, weight variation test, wetting time, disintegrating time, content uniformity, friability test etc. **Result:** Hardness, friability, weight variation, thickness and diameter of each formulation were evaluated and were found to be under the limit. Rapid disintegration within minutes was observed in all the formulations. With the addition of super disintegrants, the disintegration time increased significantly. (n=3) Based on the disintegration time, formulation F2 and F3 were found to be promising and showed a rapid disintegration time of 19±3.5sec and 25±3.0sec respectively. **Conclusion:** Mouth dissolving tablets of Levocetirizine for quick relief from allergy can be prepared by using commercially used superdisintegrants such as starch glycate and croscarmellose sodium by direct compression technique.

Keywords
Disintegration time, Levocetirizine, Orodispersible, Superdisintgrant.

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INTRODUCTION

Some patients, particularly pediatric and geriatric patients, have difficulty in swallowing or chewing solid dosage forms [1]. Alternatives for such patients include liquid-dosage preparations, effervescent and dispersible tablets and buccal orodispersible tablets (ODT) [2]. Mouth dissolving tablets also known as orodispersible tablets have the advantage of the ease of administration and rapid onset of action as saliva quickly penetrates tablet pores and causes

rapid disintegration [3-4]. ODTs are a kind of formulations that are commonly prepared using hydrophilic polymers which disintegrate enabling rapid dissolution upon contact with saliva [5].

Disintegrating agents are substances routinely included in the tablet formulations to aid in the break-up of the compacted mass into the primary particles to facilitate the dissolution or release of the active ingredients when it is put into a fluid environment [6]. The major function of disintegrates is to oppose the efficiency of the tablet binder and physical forces that act under compression to structure the tablet [7-8]. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing a high-dose drug. Generally, one gram of superdisintegrants absorbs 10- 40 g of water or aqueous medium [9]. The widely used superdisintegrants are cross-linked polyvinyl Pyrrolidone (Crosspovidone), croscarmellose Sodium and Sodium Starch Glycolate.

Levocetirizine developed from the second-generation antihistamine cetirizine is a non-sedative antihistamine and falls under the class of the third generation. It is the active R (-) enantiomer of cetirizine [10]. The hydrochloride salt form of the active levorotatory enantiomer of cetirizine, levocetirizine is a selective histamine H_1 receptor antagonist, with antihistamine, anti-inflammatory, and potential anti-angiogenic activities. It does not prevent the actual release of histamine from mast cells but prevents it from binding to its receptors. This in turn prevents the release of other allergy chemicals and increased blood supply to the area and provides relief from the typical symptoms of hay fever [10-11].

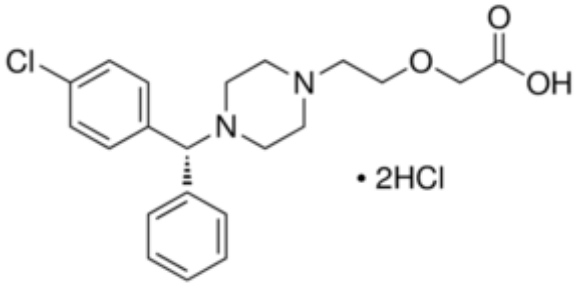

Figure 1: Chemical Structure of Levocetirizine

(2-[4-[(R)-(4Chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy]-acetic acid dihydrochloride

Oral dispersible levocetirizine tablets get easily disintegrated when comes in contact with saliva so can be administered without water can suppress the cutaneous allergic responses induced by chronic idiopathic urticaria. The study was designed to formulate levocetirizine orodispersible tablets using starch glycate and croscarmellose by direct compression technique which can be easily administered by geriatric, pediatric and bedridden patients and also improve onset of action, therapeutic efficacy and patient compliance.

MATERIALS AND METHOD

Materials:

Levocetirizine Hydrochloride was a gift sample obtained from Aadee Remedies Pvt. Ltd. Croscarmellose sodium, Polyvinylpyrrolidone, calcium carbonate, Magnesium Stearate, Talc, Sodium Starch Glycolate were purchased from Merck India. All chemicals and reagents used were of analytical grade.

Method

Altogether eight formulations of Levocetirizine tablets with varying compositions as shown in table 1 were prepared by direct compression method. The weight of tablets was set at 250 mg. The powder blend was initially studied for pre-compression parameters (solubility, linearity and calibration curve study, melting point, pH determination, Loss on drying (LOD), Organoleptic test, and drug study identification) and compressed tablets were evaluated for thickness, hardness, weight variation test, wetting time, disintegrating time, content uniformity and friability test. [10-14]

Table 1: Excipients composition for Orodispersible levocetirizine tablets

Formulation	Crosscarmellose sodium (CCS)	Starch Glycolate (SSG)	Polyvinylpyrrolidone (PVPK 30)	API	Talc	Magnesium stearate	Diluent
F1	6.9	20	1.25	5	5	5	206.85
F2	1.25	20	6.9	5	5	5	206.85
F3	12.5	20	6.9	5	5	5	195.6
F4	6.9	12.5	6.9	5	5	5	208.7
F5	6.9	5	12.5	5	5	5	210.6
F6	6.9	20	12.5	5	5	5	195.6
F7	12.5	5	6.9	5	5	5	210.6
F8	1.25	12.5	12.5	5	5	5	208.75

Preformulation Studies

Organoleptic Characterization:

Standard Levocetirizine was visually characterized for color, odor and taste.

Determination of the Melting Point

The melting point of a drug was determined by using melting point apparatus. A few quantities of a sample of the drug were filled in a thin capillary tube and were inserted at the inlet of the apparatus. The digital temperature of the instrument was increased as the instrument containing silicon oils gets heated up. Finally, the melting point of the sample is noted and recorded. This was done repeatedly three times.

Determination of Solubility

As per I.P, the solubility was determined in different solvents. First, about 5 mg of drug in 5ml of distilled water was dissolved. Similar tests were done with HCl (0.1%), phosphate buffer pH 6.8, ethanol, acetone, and chloroform. Finally, the solubility of pure drug was determined.

Preparation of standard calibration curve of Levocetirizine Dihydrochloride

The preparations of phosphate buffer are done according to IP 2010. Accurately, 28.8g of disodium hydrogen phosphate and 11.45g of potassium dihydrogen phosphate were dissolved in sufficient distilled water to produce 1000ml. 100mg of drug dissolve in 100ml of phosphate buffer solution (PBS) pH 6.8 to obtain a standard stock solution of 1000µg/ml. This standard stock solution was further diluted to obtain a working stock solution of 100µg/ml, by pipetting out 10ml in 100ml VF, and volume was made up with phosphate buffer solution. A series of dilutions were made from working stock solution, by pipetting out 1,5,10,20,50 respectively into separate 100ml of VF for each volume is made up to mark by PBS to produce concentration ranging from 1-50µg/ml. Then, the absorbance was measured at 234nm using a UV spectrophotometer. The standard curve was obtained by plotting absorbance versus concentration in µg/ml.

pH Determination

The pH meter apparatus was used to determine pH of drug. About 1% w/v dispersion of sample was shaken in water for 5 minutes (i.e. 0.5 gm in 50 ml). Then pH was determined by the use of a digital pH meter after calibrating buffer at pH 4 and pH 7.

Loss on Drying (LOD)

The hot air oven was used during the process. Here, 1gm of sample was weighted.it was then dried at 105 °C for 3 hours. It was then cooled for 30 ± 5 minutes. Then calculated using the following formula. LOD should not be more than 0.5% of its weight.

Mathematically,

$$Loss\ on\ Drying = \frac{m1 - m2}{m1 - m} * 100\%$$

Where,

Weight of weighing bottle of a sample= (m_1)

Weight of the sample and weighing bottle after drying= (m_2)

Weight of the weighing bottle dried to the constant weight= (m)

Drug Identification Studies

As per I.P, 5 mg of levocetirizine was dissolved in 10 ml of pH 6.8 phosphate buffer solution (PBS). Then was diluted in 10ml phosphate buffer sulfate. Then further volume was maintained by PBS 6.8 in 250ml of volumetric flask. In this way, the first solution was prepared. Again 10ml was pipette out from the solution first and volume was maintained by PBS 6.8. Thus, in this way, 100µg/ml solution was formed. Similarly, again 10ml of the solution was pipette out from the second solution in a 100 ml volumetric flask, and volume was maintained by PBS 6.8. Then finally 10µg/ml solution was formed. The working standard solution was prepared and scanned between 225 to

240 nm. The maximum absorbance was determined and was compared with the literature value.

Post compression Evaluation Parameters

Physical Characterization

The tablet was characterized for transparency and surface texture.

Weight Uniformity

20 tablets of mouth dissolving tablets were weighed in an analytical balance from each batch and average weighted was calculated. Then the weight variation of tablet was determined. This procedure was done as per I.P 2010.

Thickness Evaluation

The thickness was measured by placing tablet between two arms of the Vernier calipers. 5 tablets were taken and their thickness was measured.

Hardness of Tablet

The tablet hardness is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was the Monsanto hardness tester, which applies force to the tablet diametrically.

Wetting Time

A tablet was placed on a piece of tissue paper i.e. then folded twice. It is then kept in a small Petri dish (ID = 6.5) containing 6ml of water. Finally, the time for complete wetting is measured.

Disintegration Time

Here Petri dish of 10 cm diameter was filled with 10 ml of water and a tablet was put in the center of it by wrapping it into 3 fold in tissue paper. Then the time for completely disintegrating tablets into fine particles was noted.

Friability Test

As per I.P tablet strength was measured by friability tester. The first 10 tablets from each batch were weighted separately. Then the weighted tablets from each batch were placed separately in it and rotated the tester at a fixed speed of 25 rpm for 4 minutes. Then finally the tablets were dedusted and reweighted respectively.

$$\%\ \boldsymbol{friability} = \frac{(\boldsymbol{w0} - \boldsymbol{w1})}{\boldsymbol{w0}} * \mathbf{100}$$

Where,

W_0 = initial weight

W_1 = final weight

Note: the range of tablets after the use of a friability tester should be within the approved range (<1%).

Drug Content Uniformity

First, the tablets were weighed and powdered into fine particles. Then an amount of the powder equivalent to 10 mg of Levocetirizine hydrochloride was dissolved in 100 ml of pH 6.8 buffer phosphate and was filtered and diluted suitably and analyzed for the drug content at 231 nm using UV- visible spectrometer.[15]

Mathematically,

$$\text{Assay}\ \% = \frac{\text{sample absorption}}{\text{standard absorption} * \text{standard concentration}} * 100\%$$

RESULT AND DISCUSSION

Preformulation Studies of Drug

Levocetirizine hydrochloride drug powder was found to be odorless white round flat shaped with a smooth surface. The melting point of standard levocetirizine Hydrochloride was found to be 209.67±3.3^{0}C where n= 3. The levocetirizine hydrochloride was found to be insoluble in chloroform, slightly soluble in HCl but freely soluble in ethanol, acetone, distilled water and phosphate buffer which is shown in table 3.3. Preparation of standard calibration curve in phosphate buffer 6.8 yields a linear relationship in beer-lamberts plot with an equation: y=0.0165x+0.0815, R^2 = 0.996. Maximum absorption value (λ_{max}) was observed in 234 nm with linear range R^2= 0.9996. The pH was determined with help of a pH meter. The average was found to be 2.03 ± 0.027 i.e. acidic in all the formulations. Loss on drying was only 0.347% which lies below 0.5%.

Evaluation of Post compression parameter

Physical Characterization:

The physical evaluation of the tablet was done and was found to have a smooth texture with a round shape.

Evaluations of tablets

Hardness, friability, weight variation, thickness and diameter of each formulation were studied and tabulated in Table 2. The hardness range from 1.00 kg/cm2±0 to 1.67kg/cm2±0.4, friability 0.39 to 0.78 % from weight variation from 0.250-0.256% thickness from1± 0mm to 1.16mm ± 0.0489mm.

Table 2: Evaluation of post-compression parameter of orodispersible tablet

Formulations	Thickness (mm) n=5	Hardness (Kg/cm^2) n=3	Uniformity of weight (gm)	Friability (%)	Wetting time (sec)	Disintegration time (sec)
F1	1.1	1.5	0.256 ± 5%	0.68%	25±2.0	31± 2.0
F2	1.16	1.67	0.255 ± 5%	0.42%	13±1.5	19±3.5
F3	1.1	1	0.253. ± 5%	0.51%	15±2.0	25±3.0
F4	1.1	1.67	0.256. ± 5%	0.60%	43±1.5	52±2.5
F5	1	1.33	0.252 ± 5%	0.39%	47±1.5	50±1.5
F6	1.04	1.16	0.254 ± 5%	0.58%	35±2.5	41±2.5
F7	1.04	1	0.252. ± 5%	0.59%	38±2.5	49±1.0
F8	1.1	1.16	0.250. ±7.5%	0.78%	35±2.5	38±1.5

The weight uniformity of different formulations was determined Weight uniformity was determined with the help of analytical balance. All the tablets passed the weight variation test as the average percentage weight variation was within 7.5% i.e., in the pharmacopeia limits. The hardness of the tablets prepared by the direct compression method was maintained within the range of 1.00 kg/cm2±0 to 1.67kg/cm2±0.4 and was considered adequate for mechanical stability. The mean thickness was (n=5) almost uniform in all the formulations and values ranged from 1± 0mm to 1.16mm ± 0.0489mm. The standard deviation values indicated that all the formulations were within the range. Some variations in the thickness of the tablets in different formulations may be due to differences in the total excipient content.

Rapid disintegration within several minutes was observed in all the formulations. The disintegration time of fast dissolving tablets prepared by direct compression method was found to be in the range 19±3.5 to 52±2.5sec fulfilling the official requirements. With the addition of super disintegrants, the disintegration time increased significantly. (n=3) Based on the disintegration time, formulation F2 and F3were found to be promising and showed a rapid disintegration time of 19±3.5sec and 25±3.0sec respectively.

Wetting time was closely related to the inner structure of the tablet. The wetting time of Levocetirizine Dihydrochloride tablets prepared by direct compression method was found to be in the range of 13±1.5sec to sec as 47±1.5 secs as shown in the bar diagram. Promising formulations F2and F3showed a wetting time of 13±1.5sec and 15±2.0sec respectively, which facilitate the faster dispersion in the mouth. From the above data, we can conclude that as there is an increase in disintegrating time the wetting time gradually decreases.

Table 3: Drug Content Uniformity and % Friability of formulations

Formulation code	Drug content (%)	%Friability
F1	98.83	0.68%
F2	92.05	0.42%
F3	94.67	0.51%
F4	95.51	0.60%
F5	98.13	0.39%
F6	94.018	0.58%
F7	93.36	0.59%
F8	89.05	0.78%

The drug content uniformity was performed for all 8 formulations. All samples were analyzed spectrophotometrically. The percentage drugs content of the tablets was found to be between 89.05 to 98.13 % of Levocetirizine HCL. The medium was maintained at 37±0.5°C, an aliquot of dissolution medium was withdrawn at every 5 min. interval and filtered. The absorbance of filtered Solution was measured by UV spectrophotometric method at 231nm, and the concentration of the drug was determined from the standard calibration curve. The friability was found in all designed formulations in the range 0.39 to 0.78 % to all within the approved range (<1%).

For disintegration study, the polynomial equations for the formulation F1-F8 were generated using SPSS through Backward linear Regression analysis is given below:

Where $Y= 48.916 + 0.464X_1 - 1.268X_2 + 0.512X_3$

Where x_1 is CCS, x_2 is SSG and x_3 is PVPK 30 (independent variable) and Y is the time required to disintegrate (dependent variable). The positive sign of x_1 and x_3 indicates +ve effects on the time required to disintegrate. In other words, an increase in the amount of PVPK 30 and CCS, increase the time required to disintegrate.

The -ve sign of x_2 indicates the negative effects on the time required to disintegrate in other words increase in the concentration of SSG decreases the time required to disintegrate.

F_1 formulation looks 27.44 sec. to disintegrate according to the predicted equation by manipulating the concentration of CCS, PVPK30 and SSG the required time to disintegrate could be achieved.

Table 4: Comparison Between Real and predicted disintegrating time (Sec)

Formulation	CCS	SSG	PVPK30	Disintegrating time (DT) (Sec)	Predicted DT (Sec)
F_1	6.9	20	1.25	31	27.44
F_2	1.25	20	6.9	19	27.66
F_3	12.5	20	6.9	25	32.88
F_4	6.9	12.5	6.9	52	39.80
F_5	6.9	5	12.5	50	52.17
F_6	6.9	20	12.5	31	33.15
F_7	12.5	5	6.9	39	51.90
F_8	1.25	12.5	12.5	38	45.26

The effect on disintegration time and wetting time was studied by varying concentrations of commercially used Superdisintgrante (SSG, CCS) and concentration of binder (PVP K-30), which were considered. The result of the pre-compression parameter that the uniform tablets were obtained with a weight variation of ± 7.5% which complies with the IP specification limit. The result of the post-compression parameter shows that all the formulations pass friability having maximum loss of 0.78% in F8 formulations which complies with IP specifications of 1% and also assay of all the formulations was within the limit of 85 to 115%. F1 formulation was found to be the best formulation because it was disintegrated in 27.44sec which was the minimum time to disintegrate in comparison to other formulations. PVP k-30 had a positive effect on the time required to disintegrate. In other words, increasing the concentration of PVP K-30 and CCS increases the time required to disintegrate. SSG had a negative effect on the time required to disintegrate. In other words, increasing in concentration of SSG decreases the time required to disintegrate. The tablets were analyzed by evaluating wetting time, Disintegration time, hardness and thickness. It was found that disintegration time was influenced by the concentration of SSG, CCS and PVP K-30. Decreasing the concentration of PVP K-30 and increasing the concentration of SSG and CCS markedly decreases the disintegration time and vice versa. In comparing SSG and CMC, the effect of SSG on the disintegration had a better effect in an identical condition which was supported by the higher swelling index of CCS. Likewise, wetting time was influenced by the concentration of PVP K-30, SSG, and CCS.

CONCLUSION

The study indicated that variation in the amount of super disintegrant leads to varying the wetting time. The higher swelling index of starch glycate had a major effect on the wetting of Levocetirizine Dihydrochloride mouth dissolving tablet. Thus, from the study, it can be concluded that mouth dissolving tablets of Levocetirizine for quick relief from allergy can be prepared by using commercially used superdisintegrants such as starch glycate and croscarmellose by direct compression technique with increased onset of action.

ACKNOWLEDGMENT

The authors would like to thank all the faculty members and staff of Hope International College, Purbanchal University, Satdobato, Lalitpur, Nepal for their constant timely support and unreserved guidance during the study period.

CONFLICT OF INTEREST

None.

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