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Formulation and evaluation of levocetirizine dihydrochloride mouth dissolving tablets

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Abstract
Introduction: The bioavailability of some drugs may increase due to the absorption of the drug in the oral cavity. The objective of the study is used to formulate mouth dissolving tablets of levocetirizine dihydrochloride using super disintegrants like sodium starch glycollate and croscarmellose sodium which provide immediate disintegration of tablet after putting on the tongue, thereby releasing the drug in saliva.
Methods: Mouth dissolving tablets of levocetirizine dihydrochloride 5mg was formulated using croscarmellose sodium, starch glycollate, and crospovidone in different concentrations by direct compression method. Out of twenty-eight formulations designed, fifteen formulations were made by using different concentrations of super disintegration, and the remaining formulated by formulation optimization of the best batch using central composite design. Different types of evaluation parameters were determined.
Results: The formulation containing the combination of croscarmellose sodium, and sodium starch glycollate at the highest ratio showed the least disintegration time.
Conclusions: Croscarmellose sodium proves to be the most efficient disintegrants followed by sodium starch glycollate and crospovidone.

Keywords: Drug content, *In-vitro* dissolution studies, levocetirizine, mouth dissolving tablet

Introduction
United States of America food and drug administration (FDA) defines a Mouth Dissolving Tablet as a solid dosage form containing the medicinal substance(s) of active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon a tongue" [1]. Despite tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy and ease of administration lead to high levels of patient compliance [2]. The drug delivery system can significantly improve its performance in a sense of efficacy, safety, and improved patient compliance by incorporating existing medicine into a novel drug delivery system. For that advantage of Mouth Dissolving Dosage Forms or Fast Dissolving Dosage Forms are highly being recognized in the pharmaceutical industry and academic institutions [3].
The patients, especially pediatric and geriatric patients, have difficulty during swallowing or chewing solid dosage form. Pediatric and geriatric patients find difficulty to take conventional solid tablets due to fear of choking [4]. So, Mouth Dissolving Tablet is one of the most innovative oral drug delivery systems. Mouth Dissolving Tablets are also suitable for those drugs whose site of action is desired locally in the mouth such as oral ulcers, cold sores, and local anesthetic, etc. [5].
The study aims to formulate a Mouth Dissolving Tablet which comprises a therapeutically effective amount of levocetirizine dihydrochloride which disintegrates quickly in the mouth within a minute.

Methods
Levocetirizine dihydrochloride, croscarmellose sodium, sodium starch glycollate, mannitol, MCCPH 102, aerosol, aspartame, saccharin sodium, menthol, and banana flavor were received as gift samples from Curex Pharmaceutical Pvt. Ltd, Janagal VDC, Banepa, Nepal and Time Pharmaceuticals Pvt. Ltd., Nawalparasi. All the chemicals used were of analytical grade except levocetirizine dihydrochloride.

Fabrication of the tablet
All the material was weighed accurately and sieved through sieve number80. Levocetirizine dihydrochloride was mixed geometrically with MCC 102 manually. The composition of the tablet is tabulated in Table no.1 and Table no.2.

Preparation of chemical reagents

Potassium dihydrogen phosphate (0.2M): Dissolve 27.218 gm of potassium dihydrogen phosphate in water and dilute with water to 1000ml.

Sodium hydroxide solution (0.2M): Sodium hydroxide (8gm) pellets were weighed and dissolved in a 1000ml volumetric flask. Volume was then made up to the mark with distilled water.

Phosphate buffer (pH6.8): 50.00ml of potassium dihydrogen phosphate (0.2M; 2000ml) and sodium hydroxide solution (0.2M; 896ml) were mixed in plastic bucket. It was then diluted with distilled water to make up the volume up to 8 liters.

Evaluation of Tablets

Tablets were evaluated for their physicochemical parameters such as weight variation, thickness, diameter, hardness, friability, assay, disintegration time, wetting time [6], and *In Vitro* dissolution.

Preparation of standard

Levocetirizine dihydrochloride reference standard (50 mg) was weighed accurately. The drug was dissolved in phosphate buffer pH 6.8 and volume was made up to 100 ml with the same solvent. Then, 2 ml was diluted to 100 ml with the same solvent.

Preparation of sample

Twenty tablets were weighed and crushed in a mortar using a pestle. Accurately a quantity of the tablet powder (180 mg) equivalent to 5 mg of levocetirizine dihydrochloride was weighed and transferred in 100 ml volumetric flasks. Then, the samples were dissolved in phosphate buffer pH 6.8, and volume was made up to 100 ml using the same solvent. The samples were sonicated for about 15 minutes and were then filtered through Whatman filter paper. Then the filtrate 10 ml was diluted to 50 ml by using the same solvent.

Analytical Method Validation

The optimized batches of levocetirizine dihydrochloride formulated and analytical method was validated for accuracy, precision, specificity, the limit of detection, the limit of quantitation, linearity, and range.

Table 1: Composition of levocetirizine dihydrochloride Mouth dissolving Tablet using super disintegrants

Ingredients (mg/tab)	LMD 1	LMD 2	LMD 3	LMD 4	LMD 5	LMD 6	LMD 7	LMD 8	LMD 8	LMD 10	LMD 11	LMD 12	LMD 13	LMD 14	LMD 15
Levocetirizine Dihydrochloride	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Croscarmellose Sodium	4	8	12	16	20										
Sodium starch Glycollate	-					4	8	12	16	20					
Crospovidone											4	8	12	16	20
Sodium Saccharin	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Aspartame	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Menthol	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Banana Flavour	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Aerosol	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Mannitol	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
MCC-102	143	139	135	131	127	143	139	135	131	127	143	139	135	131	127
Total	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Table 2: Composition of levocetirizine dihydrochloride Mouth dissolving Tablet via formulation optimization

Ingredients (mg/tab)	LMD 16	LMD 17	LMD 18	LMD 19	LMD 20	LMD 21	LMD 22	LMD 23	LMD 24	LMD 25	LMD 26	LMD 27	LMD 28
Levocetirizine Dihydrochloride	5	5	5	5	5	5	5	5	5	5	5	5	5
Croscarmellose Sodium	5.5	1	5.5		5.5	11.86396	5.5	5.5	5.5	10	10	1	5.5
Sodium starch Glycollate	10	16	1o	10	18.4852	10	10	1.51472	10	16	4	4	10
Sodium Saccharin	1	1	1	1	1	1	1	1	1	1	1	1	1
Aspartame	1	1	1	1	1	1	1	1	1	1	1	1	1
Menthol	1	1	1	1	1	1	1	1	1	1	1	1	1
Banana Flavour	4	4	4	4	4	4	4	4	4	4	4	4	4
Aerosol	1	1	1	1	1	1	1	1	1	1	1	1	1
Mannitol	40	40	40	40	40	40	40	40	40	40	40	40	40
MCC-102	131.5	130	131.5	137	123.01	125.136	131.5	139.985	131.5	121	133	142	131.5

Results and Discussion

Physical properties of Mouth Dissolving tablets

The average weight uniformity of the tablets was found to be 199.90 to 201.50mg, which was within the range of the pharmacopeia i.e. ±7.5%. The average thickness of the tablets was within the range of 4.51mm to 4.48 mm and the diameter of the tablets was 8.10mm to 8.04 mm. To withstand mechanical shock during handling, packaging, and transportation requires a certain amount of hardness. The hardness of fabricated tablets was in the range of 4.40kg/cm^2 to4.72 kg/cm^2. The Friability of the formulation was found to be less than 1.0% i.e. within the limit as per pharmacopeia. The friability result of optimized formulation showed that can withstand abrasion in handling.

Calibration curve

The regression analysis for the linearity showed a very good correlation between absorbance at wavelength 231nm. The concentration of the solution shows that a UV-visible spectrophotometer was suitable for the analysis of dissolution in phosphate buffer pH6.8.

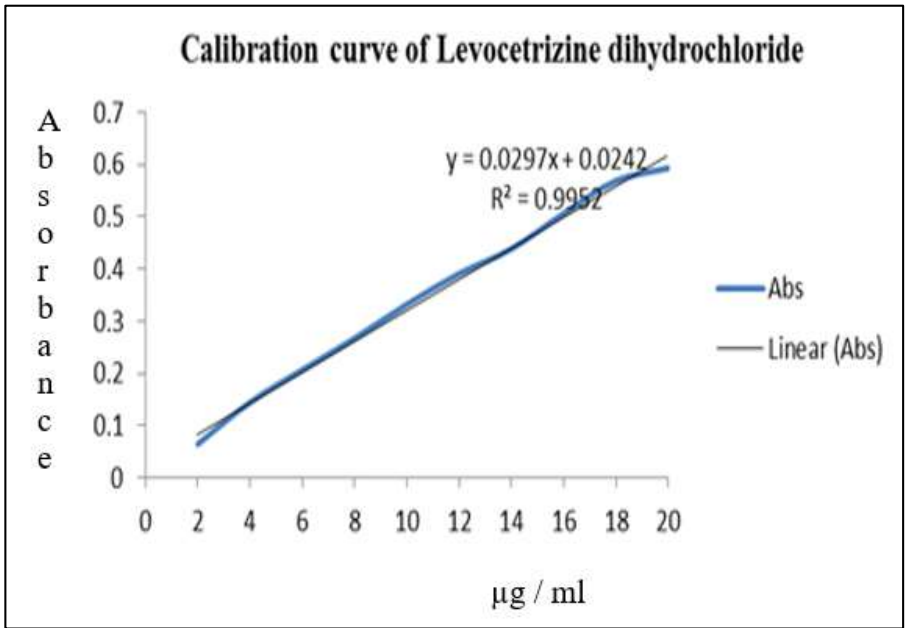

Fig 1: Calibration curve of Levocetirizine dihydrochloride

Comparative study of super disintegrants alone and in combination

Effect of single supper Disintegrants

Croscarmellose sodium: The most effective concentration was 10 % which was able to reduce disintegration time to 15secs. Unlike in other super disintegrants, disintegration time did not increase with an increase in the concentration of croscarmellose sodium. It should be due to both the wicking and swelling action of croscarmellose sodium [7, 8].

Sodium starch glycollate: The most effective concentration is 4 % which was able to reduce disintegration time to 25 seconds. There may be the formation of a viscous gel layer which may act as a thick barrier for further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents. Thus, the disintegration of the tablet was retarded to some extent when sodium starch glycollate was used as disintegrants at a high level [9, 10].

Crospovidone: The most effective concentration is 4 % which was able to reduce disintegration time to 37 seconds. There may be due to block both capillary and swelling mechanisms, destroy building up the pressure internally leading to the hindered disintegration. Thus, the disintegration of the tablet was retarded to some extent when crospovidone was used disintegrants at a high level [10].

Effect of various types of super disintegrants at the same concentration

These formulations were indicating that increasing the concentration of super disintegrants lowers the disintegrating time. Among the same concentration of 2%, 4%, 6%, 8%, and 10% of three Super disintegrants, croscarmellose sodium proved to be the most effective one, followed by sodium starch glycollate and crospovidone.

Effect of Super disintegrants on disintegration Time &Wetting Time

Effect of single supper Disintegrants

Among the different concentrations of croscarmellose sodium, the most effective formulation was found to be LMD5 followed by LMD4, LMD3, LMD2, and LMD1. LMD-05(10%) had the least disintegration time 15 seconds and the least wetting time 21 seconds. Among the different concentrations of sodium starch glycollate, the most effective concentration was found to be LMD7, followed by LMD8, LMD9, LMD10, and LMD6. LMD-07(4%) had the least disintegration time 25 seconds and the least wetting time32 seconds. Among the different concentrations of crospovidone, the most effective concentration was found to be LMD12, followed by LMD13, LMD14, LMD15, and LMD11. LMD12 (4%) had the least disintegration time 37 seconds and the least wetting time 48 seconds. All the concentrations in the formulations were found to be good. The disintegration time and wetting time were found to be within one minute. They were the best formulation among these formulations.

Combination effect of super disintegrants

The graphical representation of wetting time and disintegration time of the formulated tablet is shown in Figure 2.

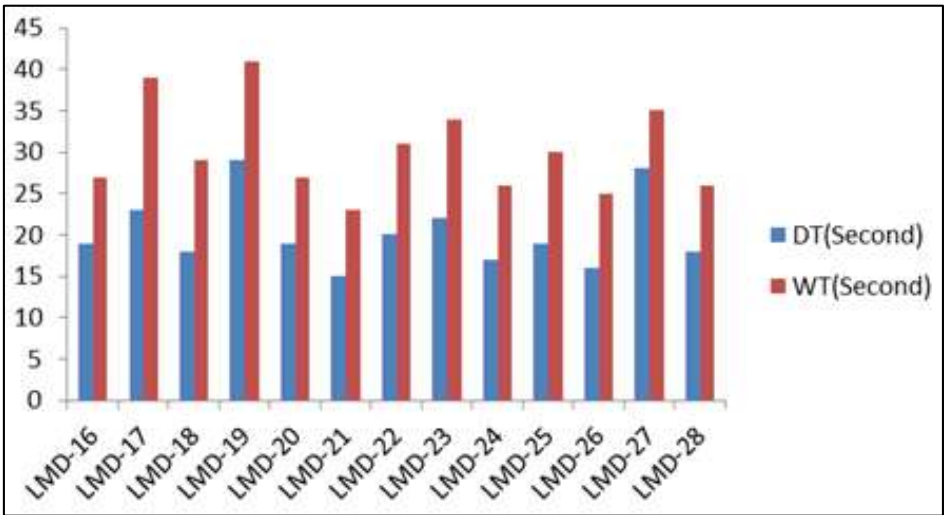

Fig 2: Comparative studies of disintegration time & wetting time of formulated batches design by central composite design

In-vitro dissolution studies

The dissolution rate was studied by using USP type-II apparatus. The dissolution of levocetirizine dihydrochloride from the tablets is shown in Figure 7. These values changed with a change in the method of preparation of tablets. In the case of tablets prepared by direct compression technique, the values decreased with an increase in the concentration of croscarmellose sodium, sodium starch glycollate, and crospovidone. The rapid increase in dissolution of levocetirizine dihydrochloride with the increase in croscarmellose sodium by disintegrants wicking due to fibrous structure swelling with minimal gelling. Due to the swelling of super disintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus reducing the disintegration and enhancing dissolution [7, 8].

Comparison of the market sample with optimized formulation

The hardness of the market sample was 3.23-3.54 kg/cm^2. The average disintegration time was 17 seconds. The drug release within 30 minutes was found 101.25%. The market sample was compared by observing the release profile at an interval of 10 minutes up to 30 minutes. The dissolution profile of marketed tablets tested by using USP dissolution apparatus II (Paddle) at 37 ± 0.5°C, 50 RPM, and 900 ml of phosphate buffer medium shown in Figure 8 Batch LMD21, and the market sample had a similar drug release profile. This showed that there is no significant difference between the release profile of formulated LMD21 and the market product.

Conclusions

Mouth Dissolving Tablets of levocetirizine dihydrochloride were successfully formulated by employing the direct compression method. Percentage weight variation and drug content uniformity were found to be within the approved range (Pharmacopoeia Standards) for all the formulations. The *in-vitro* disintegration, *in-vitro* dissolution, wetting time parameters revealed that croscarmellose sodium, sodium starch glycollate and crospovidone alone and in combinations. This acts as a super disintegrant, reveals good results in all the formulations. Among the formulation, LMD21 exhibited 102.93 % of drug release within 30 minutes and also less Disintegration time i.e. 15 seconds. Therefore, LMD21 was found to be the best formulation.

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