Original Article

Formulation and Evaluation of Rapidly Dissolving Film containing Antihistaminic drugs (Levocetirizine dihydrochloride)

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ABSTRACT

The oral dispersible tablets of Levocetirizine dihydrochloride were prepared by direct compression method. Various combinations of Sodium Starch Glycolate (SSG), Croscarmellose sodium (CCS) and Crospovidone (CP) were used as superdisintegrants for formulating the oral dispersible. It was seen that increasing the concentration of the superdisintegrants decreased the wetting time and disintegration time of the formulations. The combination of SSG & CP was more effective in decreasing the disintegration time as compared to the combination of SSG & CCS and CP & CCS. The in-vitro dissolution study showed that the formulation containing SSG (6%) and CP (4.5%) was more effective in enhancing the rate of drug release from the oral dispersible tablets. The comparison of effect of individual superdisintegrant on wetting time, disintegration time and dissolution showed that SSG was more suitable for the formulation of oral dispersible tablets of Levocetirizine dihydrochloride as compared to other superdisintegrants used in the current study. Hence, from the present study, it can be concluded that the superdisintegrants SSG and CP in appropriate concentration can be used to develop oral dispersible tablets of Levocetirizine dihydrochloride by dire ct compression method.

Key words: Orodispersible tablet, Superdisintegrants, Levocetirizine dihydrochloride, Surfactants, Starch, co-surfactants

Histamine is an organic nitrogenous compound involved in local immune responses, as well as regulating physiological function in the gut and acting as a neurotransmitter for the brain, spinal cord, and uterus. It consists of an imidazole ring attached to an ethylamine chain; under physiological conditions, the amino group of the side-chain is protonated [1].

Properties: Histamine base, obtained as a mineral oil mull, melts at 83–84 °C. Hydrochloride and phosphorus salts form white hygroscopic crystals and are easily dissolved in water or ethanol, but not in ether. In aqueous solution, the imidazole ring of histamine exists in two tautomeric forms, identified by which of the two nitrogen atoms is protonated. The nitrogen farther away from the side chain is the 'tele' nitrogen and is denoted by a lowercase tau (τ) sign and the nitrogen closer to the side chain is the 'pros' nitrogen and is denoted by the pi (π) sign. The tele tautomer, Nτ-H-histamine, is preferred in solution as compared to the pro-tautomer, Nπ-H-histamine (Fig. 1) [2].

Histamine has two basic centres, namely the aliphatic amino group and whichever nitrogen atom of the imidazole ring does not already have a proton. Under physiological conditions, the aliphatic amino group (having pKa around 9.4) will be protonated, whereas the second nitrogen of the imidazole ring (pKa ≈ 5.8) will not be protonated. Thus, histamine is normally protonated to a single charged cation. Histamine is a monoamine neurotransmitter [3].

Synthesis and Metabolism: Histamine is derived from the decarboxylation of the amino acid histidine, a reaction catalyzed by the enzyme l-histidine decarboxylase. It is a hydrophilic vasoactive amine (Figure 2). Once formed, histamine is either stored or rapidly inactivated by its primary degradative enzymes, histamine-N-methyltransferase or diamine oxidase. In the central nervous system, histamine released into the synapses is primarily broken down by histamineN-methyltransferase, while in other tissues both enzymes may play a role. Several other enzymes, including MAOB and ALDH2, further process the immediate metabolites of histamine for excretion or recycling [4].

Fig. 1 The tele tautomer (Nτ-H-histamine), on the left is more stable than the pros tautomer (Nπ-Hhistamine) on the right.

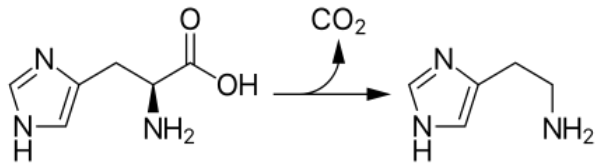

Fig. 2 -Conversion of histidine to histamine by histidine decarboxylase

Bacteria also are capable of producing histamine using histidine decarboxylase enzymes unrelated to those found in animals. A non-infectious form of foodborne disease, scombroid poisoning, is due to histamine production by bacteria in spoiled food, particularly fish. Fermented foods and beverages naturally contain small quantities of histamine due to a similar conversion performed by fermenting bacteria or yeasts. Sake contains histamine in the 20–40 mg/L range; wines contain it in the 2–10 mg/L range [5].

Mechanism of Action: In humans, histamine exerts its effects primarily by binding to G proteincoupled histamine receptors, designated H1 through H4. As of 2015, histamine is believed to activate ligandgated chloride channels in the brain and intestinal epithelium [6].

Anti-Histaminic Drugs: Antihistamines are drugs which treat allergic rhinitis and other allergies. Typically, people take antihistamines as an inexpensive, generic, over-thecounter substitutes that can provide relief from nasal congestion, sneezing, or hives caused by pollen, dust mites, or animal allergy with few side effects. Antihistamines are usually for short-term treatment. Chronic allergies increase the risk of health problems which antihistamines might not treat, including asthma, sinusitis, and lower respiratory tract infection. Consultation by a medical professional is recommended for those who intend to take antihistamines for longer-term use [7]. Although people typically use the word "antihistamine" to describe drugs for treating allergies, doctors and scientists use the term to describe a class of drugs that opposes the activity of histamine receptors in the body. In this sense of the word, antihistamines are subclassified according to the histamine receptor that they act upon. The two largest classes of antihistamines are H1antihistamines and H2-antihistamines.

Classification of anti-histaminic drugs [8]

H1-antihistamines: Meclizine, Clemastine, Hydroxyzine, Brompheniramine, Dimetindene, Doxylamine, etc. H2-antihistamines: Loratadine, Cetirizine, levocetirizine, azelastine, fexofenadine, etc. H3-antihistamines: Ranitidine, Cimetidine, Famotidine, etc.

Medical uses: Histamine produces increased vascular permeability, causing fluid to escape from capillaries into tissues, which leads to the classic symptoms of an allergic reaction- a runny nose and watery eyes. Histamine also promotes angiogenesis. Antihistamines suppress the histamine-induced wheal response (swelling) and flare response (vasodilation) by blocking the binding of histamine to its receptors or reducing histamine receptor activity on nerves, vascular smooth muscle, glandular cells, endothelium, and mast cells. Itching, sneezing, and inflammatory responses are suppressed by antihistamines that act on H1-receptors [9].

Hence, for an antihistamine drug like Levocetirizine dihydrochloride, a quick-disintegrating dosage form is suitable, since the disintegration and dissolution of the dosage form occur rapidly, thus providing a rapid onset of action. It was thought worth formulating oro-dispersible a formulations of the drug, so that the patient can ingest the dosage form anywhere and at any time, without the aid of water, which would be helpful, especially in cases of unavailability of water, motion sickness, sudden episodes of allergic attacks, and deglutition problems. Mouth-dissolving tablets of Levocetirizine dihydrochloride were prepared by a direct compression method using different concentrations of spray-dried mannitol (Perlitol SD 200), menthol, and camphor [10].

Pharmacology: Levocetirizine is an antihistamine. It acts as an inverse agonist that decreases activity at histamine H1 receptors. This in turn prevents the release of other allergy chemicals and increases the blood supply to the area, and provides relief from the typical symptoms of hay fever [11].

Clinical Data

- Trade Name :- LEVAZYL
- Other name :- Levocetirizine dihydrochloride
- Route of administration :- By mouth

Pharmacokinetics Data

- Bioavailability :- High
- Protein binding :- 90%
- Metabolism :- Liver 14%
- Elimination half-life :- 6 to 10 hour
- Excretion :- Kidney and fecal

Identification

- IUPAC:-2-(2-{4[(R)-(4chlorophenyl) (phenyl)methyl] piperazine-1yl}ethoxy)
- FORMULA :- C21H26ClN2O3
- Molar mass :- 388.89 g.mol-1

Plan of Work Formulation

1. Materials: Levocetirizine dihydrochloride was used as the active ingredient. Croscarmellose sodium, sodium starch glycolate and crosspovidone were used as the

superdisintegrants. The other ingredients used were mannitol, aerosol, magnesium sterate, aspartame, mint flavor and microcrystalline cellulose PH 102. The active drug was obtained as a gift sample from SR Drug Laboratories Pvt. Ltd, Kathamandu. Crospovidone was received as a gift sample from Lomus Pharmaceuticals Pvt. Ltd, Kathmandu. The other excipients and chemicals used in experimental works were obtained from Nova Genetica pharmaceuticals Pvt. Ltd, Dhading, Nepal. All reagents used were of analytical grade [11].

2. Methods: Preparation of orodispersible tablets of Levocetirizine dihydrochloride the composition of different formulations of Levocetirizine dihydrochloride orodispersible tablets. Levoretirizine dihydrochloride and all other excipients were weighed separately and passed through sieve number 60. The active drug was mixed with MCC PH102. Then the remaining excipients except the lubricants were blended with the active drug- MCC blend. The lubricants were then blended to the mix to form the final blend. The final blend was then compressed on a 10 stations rotary compression machine using an 8 mm punch.

3. In-vitro wetting time studies: Circular tissue papers of 10cm diameter were placed in a petri-dish containing 10 ml of buffer solution simulating saliva, pH 6.8, and amaranth. A tablet was placed on the paper and the time taken to complete it wetting it was noted. Three tablets from each formulation were randomly selected and the average wetting time was recorded [12].

4. In- vitro disintegration studies: The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. Water was used at the media for the study. The water was maintained at a temperature of 37°±0.5°C and time taken for the entire tablet to disintegrate completely was noted.

5. In- vitro dissolution studies : In vitro dissolution studies for all the fabricated tablets was carried out by using USP Type II apparatus (USP XXIII Dissolution Test Apparatus) at 50 rpm in 900 ml of phosphate buffer pH 6.8, maintained at 37±0.5ºC. 5 ml aliquot was withdrawn at the specified time intervals, filtered through Whatmann filter paper and assayed spectrophotometrically at 231nm using dissolution medium as blank. An equal volume of fresh medium, which was pre-warmed at 370C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. Dissolution studies were performed in triplicate. Then the cumulative percentage of drug release was calculated using the following formula [12].

Results & Evaluation

1. Evaluation of films Thickness: All the batches were evaluated for thickness by using a calibrated digital micrometer. Three readings from all the batches were taken and the mean thickness was evaluated at 10.

2. Folding endurance: The folding endurance was measured manually on the prepared films. A strip of film was cut and repeatedly folded in the same place till it broke. The number of times the film could be folded in the same place without breaking gave the value of folding endurance to 11.

3. Drug content: The drug content of all nine batches was determined by the UV-spectrophotometric method. For this, a 1.4x1.2 cm2 strip from each batch was cut and dissolved in 50ml of methanol. Then 5 ml of this solution was diluted to 50 ml. So a 4ppm solution was made, filtered and absorbance was recorded at 231 nm in comparison with the 4ppm standard solution. Drug content was calculated by comparison method 10.

4. Uniformity of drug content: For determining the uniformity of drug content in the film at least 10 strips (1.4x1.2 cm2) ware taken and assayed. Same procedure was repeated for all the 6 batches 10.

5. In vitro disintegration time: The disintegration test was performed on the USP disintegration time testing apparatus. Simulated salivary fluid (pH 6.8) was used as a medium. The films were placed in the tubes of the container and the disks were placed over it.

6. Bursting strength: It is also known as tensile strength. It is the maximum tolerance power of an oral fast dissolving film. How many grams of weight when applied through a pointed subject in the film will be the bursting strength of that film?

7. Moisture permeation: This test is to check weather a film is moisture permeable or not. For this in a vial desiccated silica was kept, and on the mouth of vial oral film was bounded and placed in 90% RH for 2 days.

8. In-vitro dissolution studies: Dissolution study was carried out in USP basket type apparatus using the stimulated salivary fluid (pH 6.8) as a dissolution medium at 50 rotations per minute. 10 ml aliquots were withdrawn at one-minute time intervals and same amount of fresh dissolution medium was added. The aliquots were assayed for drug content at 231nm wavelength using UVspectrophotometer. The cumulative percentage drug release was calculated.

DISCUSSION

The comparison of the effect of individual superdisintegrants on the wetting time, disintegration time and dissolution showed that SSG was more suitable for the formulation of oral dispersible tablets of Levocetirizine dihydrochloride as compared to other superdisintegrants used in the current study. Hence, from the present study, it can be concluded that the

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CONCLUSION

The oral dispersible tablets of Levocetirizine dihydrochloride were prepared by direct compression method. Various combinations of Sodium Starch Glycolate, Croscarmellose sodium and Crospovidone were used as the superdisintegrants for formulating the oral dispersible. It was seen that increasing the concentration of the superdisintegrants decreased the wetting time and disintegration time of the formulations. The combination of SSG & CP was more effective in decreasing the disintegration time as compared to the combination of SSG & CCS and CP & CCS. The in-vitro dissolution study showed that the formulation containing SSG (6%) and CP (4.5%) was more effective in enhancing the rate of drug release from the oral dispersible tablets.

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