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Research Article

FORMULATION DEVELOPMENT AND CHARACTERIZATION OF EFFERVESCENT TABLETS ALONG WITH LEVOCETIRIZINE DIHYDROCHLORIDE

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ABSTRACT

Objective: Levocetirizine dihydrochloride is also known as "Xyzol." Levocetirizine dihydrochloride is a second-generation piperazine derivative, potent H1 selective agent. Levocetirizine dihydrochloride is the active R (-) enantiomer of cetirizine dihydrochloride. In the case of an allergic or histaminic reaction, the medication must respond rapidly. Many older patients, infants, and dysphagia patients have trouble swallowing traditional tablets or capsules. Hence, a need exists for a relatively fast-acting effervescent tablet form.

Methods: The tablets were prepared by direct compression method using citric acid and sodium bicarbonate as effervescent agents. Then, they were tested for parameters of pre- and post-compression. Tablets were evaluated for studies of general appearance, uniformity of substance, hardness, friability, and *in vitro* dissolution.

Results: More than 90% of the drug was released from almost all the formulations within 1 min. More formulations underwent rapid 90-day stability trials.

Conclusion: No major changes in the taste, disintegration, and dissolution profiles were found in tablets.

Keywords: Levocetirizine dihydrochloride, Effervescent tablet, Direct compression method, citric acid, Sodium bicarbonate.

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INTRODUCTION

Various first-generation antihistamine drugs can be used in the treatment of allergy but not used because they cause sedation although initial second-generation drugs-like terfenadine and astemizole were found effective in allergic rhinitis and idiopathic urticaria without any sedation but had cardiac associated interactions. Other second-generation medications such as loratadine and cetirizine show efficacious in the treatment of allergic rhinitis and chronic idiopathic urticaria [1]. Levocetirizine dihydrochloride is a drug that comes under the category of second-generation antihistamine, and it an enantiomer levorotatory (-) form of cetirizine which is pharmacologically active and most selectively inhibit H_1 histamine receptor [2]. Chemically levocetirizine dihydrochloride is (R)-[2-[4-[(4-chlorophenyl) phenylmethyl)-1-piperazinyl] ethoxy] acetic acid dihydrochloride. It is having the same pharmacological activity as cetirizine but produces less sedation as compared to cetirizine and thus more preferred nowadays [3]. Interestingly, levocetirizine has many other pharmacological consequences, partly linked to its H-1 antagonism. T lymphocytes, dendritic cells, and lung macrophages express the H-1 histamine receptor on their cell surface that induces activation molecules and cytokine and chemokine synthesis with proinflammatory effects when enabled [4]. It shows inhibitory action on keratinocytes, and also blocks the secretion of chemocytokine and granulocyte-macrophage colony-stimulating factor [5]. It is administered orally and achieves peak plasma concentration after 0.9 h of administration. On single and repeated 5 mg/day indicates the peak concentrations typically 270 ng/mL and 308 ng/mL, respectively, when levocetirizine dihydrochloride in the form of solution orally administered to an adult, the mean peak plasma concentration achieved in 0.5 h after administration. Protein binding *in-vivo* is about 91–92%. About <14% of levocetirizine dihydrochloride metabolized in the body by different metabolic reactions. In healthy adult, plasma half-life is 8–9 h of levocetirizine dihydrochloride after administration in the form of oral tablet and oral solution. Adverse effects include fatigue, dry mouth, somnolence, pharyngitis, cough, and pyrexia. On overdose sigh and symptoms include drowsiness, agitation, and restlessness, so symptomatic treatment can be done, no antidote therapy is available for the overdose of levocetirizine dihydrochloride [6].

The oral route of drug administration is the most important and convenient method of administering the drug. Probably at least 90% of all the drugs used to produce the systemic effects are administered by the oral route. When a new drug is discovered, the pharmaceutical company makes every effort to ensure that the drug can be so formulated that it is capable of being administered orally. However, most elderly patients, children, and patients with dysphagia have difficulty in swallowing conventional tablets and hard gelatin capsules, and therefore do not take medication as prescribed by physicians. It is estimated that 35% of the general population, 30–40% of elderly nursing home patients, and 25–50% of patients hospitalized for acute neuromuscular disorders and head injuries have dysphagia [7]. Hence, the efforts are being made by the researchers in the field of novel drug delivery systems to overcome these above problems and enhance the efficacy, safety, and stability of the drug molecule and also improved patient compliance [8]. Effervescence is defined as the evolution of bubbles of gas from a liquid as the result of a chemical reaction. Effervescent mixtures have been known for many years and are used medicinally. Effervescent powders utilized as saline cathartics were available in the 18th century and were then listed in the official compendium as compound effervescent powders. These were more commonly known commercially as "Seidlitz Powders." When tableting equipment was developed, these granular materials began to be compressed into tablets that offer some advantages over the powdered dosage forms. Effervescent tablets are effective, simple to use, and premeditated ways of dosage. The powdered preparations cannot leak out as they can.

These can be individually packed to prevent moisture and thereby avoid the issue of product instability during storage of the unused products. Throughout the years, a large range of effervescent tablets has been developed. These include formulations containing antioxidants, contact lens cleaners, washing powder formulations, beverage sweetening pills, chewable dentifrices, denture cleaners, surgical instrument sterilizers, analgesics, effervescent candy, and other prescription medication preparations such as antibiotics, ergotamine, digoxin, methadone, and L-dopa. Preparations have also been established for veterinary use. Effervescent tablets are not meant to be ingested or used without prior dissolution, usually in water, which leads to rapid absorption and onset of action [9]. The overall use of the tablet solution plays a major role in product formulation, especially in choosing the raw materials to be used. Some substances have useful properties in tablet formulation, the solutions of which are not ingestible while at the same time possessing additional properties which make them useless if the solution is to be ingested (i.e., boric acid as a tablet lubricant, sodium bisulfite as an acid source, or sodium bicarbonate as a source of carbon dioxide in a sodium-free potassium supplement) [10]. Effervescent tablet having certain advantages on other types of tablets, which includes having pleasant taste due to which improved patients acceptance, a large amount of drug can be administered, ease of use, accurate dosing, also having good stomach and intestinal tolerance. An effervescent tablet can easily administer to the child, adults, and older age patients [11].

The objective of this study was that to increase the efficacy, safety, and stability of dosage form, and to overcome the problems with the conventional solid dosage form means tablet. In this study, the effervescent tablet of levocetirizine dihydrochloride had been developed and evaluated before compression (and after the compression). In this technique had been used direct compression of evaluated granules. Effervescent tablets of levocetirizine dihydrochloride are not available [12].

MATERIALS AND METHODS

Methods

Preformulation studies

The objectives of preformulation studies are to select the correct form of the drug substance, assess its physical and chemical properties, and generate a thorough understanding of the stability of the material under the conditions that will lead to the development of a particular Data Distribution Service.

The goals of the preformulation study are:

- To determine the physicochemical characteristics required for a new drug product
- To assess the rate of its kinetic release
- To assess compatibility with different excipients.

Preformulation studies on the drug sample obtained, therefore, cover color, taste, solubility analysis, melting point determination, and compatibility studies [13].

Identification of levocetirizine dihydrochloride

1. Melting point determination: Melting point of levocetirizine dihydrochloride was set to determine by open cup capillary method
2. Infrared absorption spectrum: The infrared absorption spectrum of levocetirizine dihydrochloride was recorded with a KBr disc.

Preparation of standard calibration curve of levocetirizine dihydrochloride in 0.1 N hydrochloric acid (HCl).

Procedure

One gram of sodium bicarbonate was accurately weigh and transferred it into 100 ml amber colored volumetric flask and dissolved in a small quantity of 0.1 N HCl. To this, a solution 100 mg of levocetirizine dihydrochloride dissolved in approximately 2–5 ml of water was added. To get a concentration, the volume was composed with the 0.1 N HCl of 1000 µg/ml (standard stock -I [SS-I]).

From this, 1 ml was separated and diluted to 100 ml to obtain a concentration of 10 µg/ml (SS-II). From SS-II aliquots of 2 ml, 4 ml, 6 ml, 8 ml, and 10 ml were pipette out into 10 ml volumetric flasks. The volume was made up with 0.1 N HCl to get the final concentration of 2, 4, 6, 8, and 10 µg/ml, respectively. When scanning the solution in the ultraviolet (UV) range, that is, from 200 nm to 800 nm λ_{max} was found to be 230 nm for levocetirizine dihydrochloride in 0.1N HCl as a blank in UV-visible spectrophotometer (UV-1800 Shimadzu). The absorbance of each concentration was measured at 230 nm.

The same solution was stored at room temperature and absorbances of the solutions were measured at 230 nm using a UV-visible spectrophotometer after every ½ h.

Beer's range: 2–100 µg/ml.

Formulation of effervescent tablets of levocetirizine dihydrochloride

Levocetirizine dihydrochloride effervescent tablets were prepared using direct compression method:

All ingredients were individually passed and retrieved through 60 # mesh sieve. The drug was weighed along with the other excipients and was mixed in geometrical order. Sodium bicarbonate and citric acid were pre-heated at a temperature of 80°C for 2 h to remove absorbed/residual moisture and thoroughly mixed in a mortar to get a uniform powder, then transferred to the blend above. Magnesium stearate and Aerosil were added at last and this mixture was shaken for few minutes to ensure proper mixing of all the ingredients. The blend thus obtained was directly compressed into tablets of 200 mg weight on a 10-station rotary tablet machine (Clit, Ahmadabad) using 7 mm round flat punches.

Evaluation of effervescent tablets

Pre-compression parameters

The mixture of powder and granules was evaluated before compression and parameters include the angle of repose for flow property, bulk density, Carr's compressibility index, and Hausner's ratio.

Angle of repose (ɵ)

The angle of rest is known as the maximum possible angle between the surface of a powder pile and the horizontal plane [14]:

Tan^{-1} (h/r)

Where, angle of repose,

h = height of the pile.

r = radius of the base of the pile.

Bulk density

The bulk density is defined as a powder mass divided by the volume of the bulk. The bulk density of a powder depends primarily on the distribution of particle size, the particle form, and the propensity of the particles to conform to each other and the particle packaging and changes as the powder consolidates. Tap density tester was used to assess both loose bulk density (LBD) and tapped bulk density (TBD). LBD and TBD were calculated using the following formula [15,16]:

Bulk density = Weight of the powder/tapped volume of powder

Carr's compressibility index

Carr's compressibility index determined the compressibility value for the granules. The formula for Carr's index is as follows [17]:

Compressibility index (%) = [(TD-BD) × 100]/TD

Where TD = tapped density, and

BD = Bulk density.

Hausner's ratio

It is used to determine the flow property and is also a type of index. It can determine by the following formula:

Hausner's ratio tapped density/bulk density

Evaluation of tablets

After the direct compression of evaluated granules, the tablets are subjected for evaluation that is shape and color, uniformity of thickness, hardness test, and friability test.

Shape and color

The tablets were analyzed under a lens by holding the tablets in light for tablet form and color.

Uniformity of thickness

The individual tablet's crown thickness can be determined with a Vernier Caliper, which allows precise measurements and provides details on the difference between tablets. Many techniques used in production control involves positioning 5 or 10 tablets in a holding tray, where a sliding caliper scale may be used to measure their total crown thickness. The thickness of the tablet was measured using Vernier Caliper [18].

Hardness test

Tablets need to have a certain amount of strength, or hardness and friability protection, to withstand mechanical handling shocks in manufacturing, packaging, and shipping. The tablet's hardness has been determined using a Monsanto Hardness tester. It is expressed in kg/cm^2. Three tablets were chosen randomly from each formulation, calculating the mean and standard deviation values [19,20].

Weight variation test

From each formulation, the tablets were picked at random and weighed individually to test for weight variability. The U.S Pharmacopoeia makes a small variance of a tablet's weight [21]. The percentage deviation in weight variation is shown in Table 5.

The tablet weight was more than 130 mg and <324 mg in all formulations and therefore a maximum difference of 7.5% was allowed.

Friability test

This is the phenomenon where tablet surfaces are weakened and/or when exposed to mechanical shock or fatigue, show signs of lamination or breakage. Using Roche Friabilator, the friability of the tablets was calculated. It is expressed in percentage (%). Initially, ten tablets were weighed [W (initial)] and put into a friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again [W (final)]. The percentage friability was then calculated by,

Drug content uniformity

The uniformity examination of content is used to confirm that each tablet contains the amount of drug substance intended for a batch, with little difference between tablets. The content uniformity analysis has been included in the monographs of both coated and uncoated tablets designed for oral administration due to a better understanding of clinical availability where the range of size of the dosage type available involves 50 mg or smaller sizes. Representative samples of 30 tablets are chosen for content uniformity evaluation, and 10 are randomly tested. At least 9 must be evaluated below ±15% of the stated power, but none should cross ±25% [22,23].

The amount of active ingredient(s) is estimated by the process mentioned in the assay and it estimates the amount of active ingredient since the active ingredient of the present investigation is not official in any pharmacopeia the following method was used for the determination of drug content [24].

Twenty tablets were weighed and powdered. The blend equivalent to 20 mg of pantoprazole sodium was weighed and dissolved in a sufficient quantity of 0.1N HCl. The solution was filtered through Whatman filter paper (No.41), suitably diluted with 0.1N HCl and assayed at 230 nm, using a UV-visible double beam spectrophotometer (UV-1800 Shimadzu).

Table 1: Formulation of effervescent tablets of levocetirizine dihydrochloride

S. No.	Ingredients	Quantity used in mg					
		F1	F2	F3	F4	F5	F6
1.	Levocetirizine	5	5	5	5	5	5
2.	Sorbitol	30	30	30	30	30	30
3.	Sodium bicarbonate	20	50	50	30	50	60
4.	Citric acid	60	50	30	50	50	20
5.	Mannitol	47	32	32	32	27	47
6.	Crospovidone	12	10	8	6	14	10
7.	CCS	8	10	12	14	6	10
8.	Aspartame	15	10	10	10	15	15
9.	Aerosil	1	1	1	1	1	1
10.	Magnesium stearate	2	2	2	2	2	2

Table 2: Flow properties of the powder according to their angle of repose

Angle of repose (ɵ) (degrees)	Flow
<25	Excellent
25=30	Good
30–40	Passable
>40	Very poor

Table 3: Flow properties of the powder, according to Carr's index

Consolidation index (Carr's %)	Flow
5–15	Excellent
12–16	Good
18–21	Fair to passable
23–35	Poor
33–38	Very poor
>40	Very very poor

Table 4: Flow properties of powders, according to Hausner's ratio

HR	Flow
<1.2	Free-flowing powder
>1.6	Less free-flowing

Table 5: Percentage deviation in weight variation

Average weight of a tablet	Percentage deviation
<130 mg	10
130–323 mg	7.5
324 mg and above	5

In-vitro disintegration time

A tablet's process of breaking up into smaller particles is called as disintegration. A tablet's *in vitro* disintegration period was calculated using a standardized disintegration test which was used only for rapid disintegration agents [25].

Methods

The disintegration took place in a beaker which included a 200 ml medium. The medium consisted of water at a temperature between 15 and 25°C. Just one tablet was tested at a time and was deemed disintegrated when fragments were obtained fully dispersed [26,27].