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.

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 H1 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 chemokytokine 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 "Sciditz Powders." When tabulating 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 LSD. 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 ingerible 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). 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, 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 weighed 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 composited 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 λmax was found to be 230 nm for levocetirizine dihydrochloride in 0.1N HCl as a blank in UV-Visible spectrophotometer (UV-1800 Shim.adz). 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 (Glt, 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 (α)

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

$$\tan^{\circ} \left(\frac{h}{r}\right)$$

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]:

$$\text{Bulk density} = \frac{\text{Weight of the powder}/\text{tapped volume of powder}}{\text{Volume of the powder}}$$

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]:

$$\text{Compressibility index (%)} = \frac{\text{TD-BD} \times 100}{\text{TD}}$$

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:

$$\text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$
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/cm². 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 US 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 Friability, 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,

\[ \text{Consolidation index (Carr's %)} = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100\% \]

**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 ±1.5% of the stated power, but none should cross ±2.5% [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 Pharmacopoeia 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).

**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].
**In vitro dissolution studies**

In vitro release studies were carried out using a USP XXIII type-II dissolution test apparatus.

Two aims in the design of in vitro dissolution tests are to demonstrate that,
1. The release of the drug from the tablet is up to 100% as near as possible
2. The rate of release of drugs is standardized from batch to batch, which is the same as the rate of release shown to be bioavailable which clinically efficient [28].

**Methods**

The normal USP XXIII type-II dissolution apparatus was used employing a paddle stirrer at 50 rpm. As a dissolution medium, 900 ml of the pH 6.8 phosphate buffer was used. The temperature of the dissolution medium was maintained at 37±0.5°C throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5 ml) were withdrawn using a syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 230 nm. The volume withdrawn was filled with a fresh volume of dissolution medium at each interval of time. Cumulative percent of levocetirizine released was calculated and plotted against time [29,30].

**Stability studies**

A drug’s stability was characterized as the potential of a particular formulation to remain within its physical, chemical, therapeutic, and toxicological specifications in a particular container. Stability studies were conducted as per the specified ICH guidelines, the selected best formulation. The goal of the stability testing was to provide evidence as to how the nature of a drug material or drug product changes with time under the influence of various environmental factors, such as temperature, humidity, and sunlight, enable appropriate storage standards, re-test duration, and shelf life to be determined.

In the present study, the effervescent tablets were packed in suitable packaging material and stored under the following conditions for a period of 90 days at 40±2°C and RH 75±5%.

The tablets were withdrawn and analyzed for physical characterization (visual defects, hardness, friability, disintegration, dissolution, etc.) and drug content [31].

**RESULTS AND DISCUSSION**

The present study was aimed at formulating effervescent tablets of levocetirizine dihydrochloride. This is a novel approach to improving patient compliance with a rapid onset of action as opposed to traditional formulations that are currently primarily used.

**Identification of levocetirizine dihydrochloride**

**Melting point**

The melting point of levocetirizine dihydrochloride sample was found to be 218.5°C.

**Fourier-transform infrared (FTIR) studies**

FTIR is one of the most widely used methods for checking the compatibility between substances and for the identification of the drug. Levocetirizine dihydrochloride, excipients, and the selected formulations were analyzed using an infrared spectrophotometer (Shimadzu FTIR 8-400, S model).

All of the samples were screened using the KBr disk method at a resolution of 4 cm⁻¹ over the wavenumber range of 4000–400 cm⁻¹. These KBr disks are developed in a ratio of 1:100, respectively, using drug and KBr. Then, this mixture was mixed well in mortar for 3–5 min. A very small amount of this mixture was uniformly spread and sandwich between the pellets and pressed using KBr pellet press at a pressure of 20,000 psi for 1 min. Then, the pressure was released and the pellet was inserted into the pellet holder and scanned in the IR zone.

The drug sample FTIR spectroscopy had shown the identical peak characteristics as that of the levocetirizine dihydrochloride standard which verified that our drug sample was levocetirizine dihydrochloride.

**Solubility of drug**

Levocetirizine dihydrochloride solubility was calculated in various solvents that were listed in the Table 8 as follows.

Levocetirizine dihydrochloride was freely soluble in water, soluble in ethanol, methanol, and HCl and insoluble in methylene chloride and acetone.

**Standard calibration curve**

**Preparation of calibration curve of levocetirizine dihydrochloride**

**Evaluation**

**Pre-compression parameters**

The results of angle repose, bulk density, tapped density, and compressibility index evaluation for different blends of formulations shown in Table 10.

The results of the evaluation of pre-compression parameters showed that varies from compressibility index 8.72±0.53% to 15.65±0.53% and angle of repose varies from 16.36±0.59° to 20.33±0.71°. Thus, all formulation blends comprised excellent flow as well as very good compressibility profile which are a prime requisite for direct compression.

**Post-compression parameters**

**Physical appearance**

Uncoated white-colored tablets are round, flat, and plain in appearance.

| Percent friability | Acceptable limit |
|-------------------|------------------|
| <1                | Acceptable       |
| >1                | Not acceptable   |

**Table 6: The acceptable limit of friability, according to Indian Pharmacopoeia**

| Peak | Theoretical (cm⁻¹) | Standard (cm⁻¹) | Drug sample (cm⁻¹) |
|------|-------------------|----------------|--------------------|
| -O   | 740–880           | 758, 804, 847  | 758.05, 808.20, 844.85 |
| -C-N | 1350–1390         | 1362           | 1356               |
| -COOH| 1730–1790         | 1742           | 1742.05            |
| -C-O | 1120–1170         | 1134           | 1136.11            |

**Table 7: Characteristic peak with their functional group**

**Table 8: Solubility of levocetirizine dihydrochloride in different solvent systems**
Values are means±SEM, for **n=3, ***n=6 and ****= values in range

The prepared tablets from all six formulations were subjected–post-compression parameter, that is, thickness, diameter, average weight, uniformity of weight, and drug content. All the post-compression parameters of all the formulations were compared with the compendial specification for effervescent tablets. The results are shown in Table 11.

The post-compression test results of various tablet formulations indicated that the thickness for all the formulation ranged from 3.03±0.119 to 3.12±0.32 mm and from 8.00±0.010 to 8.06±0.041 mm in diameter.

The hardness for all the formulation was varied from 2.5±0.35 to 3.3±0.28 kg/cm². Overall there was no significant change in this parameter which indicates that blending was uniform.

The disintegration time was significantly improved with an increase in concentration in super disintegrants, which ultimately affect the dissolution of the drug.

Stability studies for optimized formulation

Accelerated stability studies are carried out on the optimized batch (F6). The batch was evaluated at the intervals of 1 month and 3 months, respectively, at 40±2°C and 75±5%RH. The formulation F6 (tablets) was subjected for the evaluation of physical parameters such as description, thickness, diameter, average weight, weight uniformity, hardness, friability, taste, drug content, disintegration time, and in-vitro drug release.

| S. No. | Concentration (µg/ml) | Absorbance |
|--------|-----------------------|------------|
| 1.     | 0                     | 0          |
| 2.     | 4                     | 0.121      |
| 3.     | 8                     | 0.258      |
| 4.     | 12                    | 0.375      |
| 5.     | 16                    | 0.490      |
| 6.     | 20                    | 0.623      |
| 7.     | 24                    | 0.742      |

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Table 10: Results of pre-compression evaluation of formulation blend

| Formulation | Bulk density (g/cm³) | Tapped density (g/cm³) | Compressibility index (%) | Angle of repose (θ) |
|-------------|----------------------|------------------------|---------------------------|---------------------|
| F1          | 0.95±0.010           | 1.14±0.057             | 15.65±0.53                | 20.33±0.71          |
| F2          | 0.95±0.051           | 1.09±0.045             | 13.30±0.48                | 19.03±0.31          |
| F3          | 0.94±0.053           | 1.07±0.015             | 12.29±0.44                | 17.5±0.25           |
| F4          | 0.93±0.057           | 1.05±0.057             | 11.16±0.46                | 16.77±0.15          |
| F5          | 0.93±0.056           | 1.03±0.058             | 9.66±0.85                 | 16.3±0.16           |
| F6          | 0.93±0.058           | 1.03±0.055             | 10.25±0.47                | 16.3±0.59           |

*Values are means±SEM, n=3

Table 11: Results of post-compression evaluation of effervescent tablets

| Formulation | Thickness (mm) *** | Diameter (mm) *** | Average weight (mg) | Uniformity of weight (%) **** | Hardness (kg/cm²) *** | Friability (%) ** | Drug content (%) **** | DT (s) ** |
|-------------|--------------------|-------------------|---------------------|-----------------------------|----------------------|------------------|----------------------|-----------|
| F1          | 3.0±0.031          | 8.02±0.836        | 200.60              | -4.4±2.6                    | 2.5±0.35             | 0.72±0.025        | 98.23±99.62         | 22.00±4.39 |
| F2          | 3.09±0.054         | 8.04±0.418        | 206.50              | -3.2±1.4                    | 2.7±0.23             | 0.60±0.021        | 97.76±102.13        | 21.50±3.10 |
| F3          | 3.05±0.010         | 8.06±0.041        | 198.25              | -3.6±2.2                    | 3.1±0.41             | 0.45±0.015        | 99.33±99.13         | 20.00±5.09 |
| F4          | 3.03±0.119         | 8.04±0.014        | 199.02              | -1.6±1.1                    | 3.2±0.27             | 0.35±0.025        | 95.56±98.16         | 18.00±4.96 |
| F5          | 3.12±0.327         | 8.00±0.010        | 201.45              | -2.5±1.5                    | 3.3±0.28             | 0.33±0.02         | 99.16±102.29        | 22.75±2.98 |
| F6          | 3.08±0.277         | 8.04±0.089        | 200.67              | -2.1±1.3                    | 3.1±0.22             | 0.35±0.03         | 98.81±100.60        | 18.00±4.61 |

*Values are means±SEM, n=3

Table 12: Results of in-vitro drug release study of effervescent tablet formulations

| Time (min) | Cumulative percent drug released |
|------------|----------------------------------|
|            | F1                               | F2                               | F3                               | F4                               | F5                               | F6                               |
| 2          | 11.3±1.66                        | 10.63±2.24                       | 12.72±3.25                       | 13.99±1.95                       | 13.84±1.41                       | 14.36±2.32                       |
| 5          | 40.8±3.52                        | 43.39±2.30                       | 46.27±4.27                       | 50.51±1.32                       | 54.68±0.74                       | 59.84±1.52                       |
| 10         | 73.5±3.09                        | 78.72±2.16                       | 79.57±2.52                       | 85.33±1.01                       | 91.57±0.59                       | 91.86±1.20                       |

*Values are means±SEM, n=3

There had been no major change in physical parameters, product quality, and the levocetirizine dihydrochloride effervescent tablet formulation (F6) cumulative product release profile stored at 40±2°C/75±5 percent RH when compared from the same formulation before storage.

CONCLUSION

In the present work, an attempt was made to prepare an effervescent tablet of levocetirizine dihydrochloride. Effervescent tablets have an advantage over conventional tablets in elderly, pediatric patients with dysphagia.

The parameters of pre- and post-compression of all formulations were evaluated. The effect of formulation variables such as different classes of super disintegrants in varying ratios on various pre- and post-parameters was evaluated using parameters such as disintegration time, uniformity of weight, content uniformity, friability, hardness, thickness, and stability studies.

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AUTHORS’ CONTRIBUTIONS

The authors announce together declares that all have contributed toward this research work. All the studies conducted by all the authors together.

CONFLICTS OF INTEREST

The authors announce that there are no conflicting interests concerning this work and its publication.
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