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Research Paper

Evalution and Development of Antidiabetic Effervescent Tablet of Caffeine

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ABSTRACT

Researchers have emphasized the beneficial effects of coffee drinking on blood sugar management in humans. Conversely, the common medication used to treat type 2 diabetes is metformin. The purpose of this study was to investigate potential uses of coffee as an adjuvant to metformin or as a stand-alone treatment for type 2 diabetes Serum HbA levels were considerably lower in groups treated with black coffee (Group 3), metformin (Group 4), and black coffee with metformin (Group 5) than in the 1C diabetic control group (Group 2) ($P<0.05$).Acceptable salt of metformin, an acid compound or acid salt, an alkaline effervescing compound, one or more compressible binders, and one or more excipients are the components of the effervescent composition of metformin that is the subject of the invention. The weight ratio of the acid compound or acid salt (b) to the alkaline effervescing compound (c) must be greater than 2:1. Tablets and granules made from them are likewise covered by the invention. The invention also pertains to methods for producing effervescent tablets and granules, as well as a method for preparing said composition. The invention specifically targets formulations of metformin hydrochloride as well as the tablets and granules derived from them.

INTRODUCTION

Effervescent tablets offer both qualities of solid and liquid dosage forms. The tablets are administered as a liquid after being distributed and dissolved in water. Although the medicine is presented as a tasty liquid, it nevertheless has the benefits of a solid dosage form, including simple mobility, long stability, and dose precision (Khan et al., 2014; Mohammed et al., 2016). The convenience of use of this dosage type is contributing to its growing popularity. The tablet frequently turns into an effervescent solution when the buoyant delivery mechanism breaks when it comes into touch with water (Agyilirah et al., 1991; Saleh SI et al., 1988). Nonetheless, during production and storage, the dosage forms are

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subject to numerous crucial factors. Effervescent tablets are susceptible to chemical reactions because of their early effervescent reaction. Many of the components are hygroscopic. Additionally, the presence of a trace amount of water starts a self-propagating reaction that lasts until the product's quality completely deteriorates (Harald, 2003). Accordingly, the preparation processes ought to be conducted in a temperature and humidity-controlled setting (Khan et al., 2014; Josep et al., 2011; Osei-Yeboah et al., 2014).

Caffeine changed blood glucose maintenance in diabetic males, as evidenced by its ability to raise insulin and serum glycemia levels following an oral glucose tolerance test (OGTT). Insulin sensitivity as measured by insulin sensibility index (ISI) rates decreased. demonstrated the ability of caffeine treatment to regulate catecholamine levels. Long-term caffeine use, however, has been shown to be effective in regulating blood glucose adiponectin levels, which is beneficial for both preventing and treating the release.

Machanism of action of caffeine:

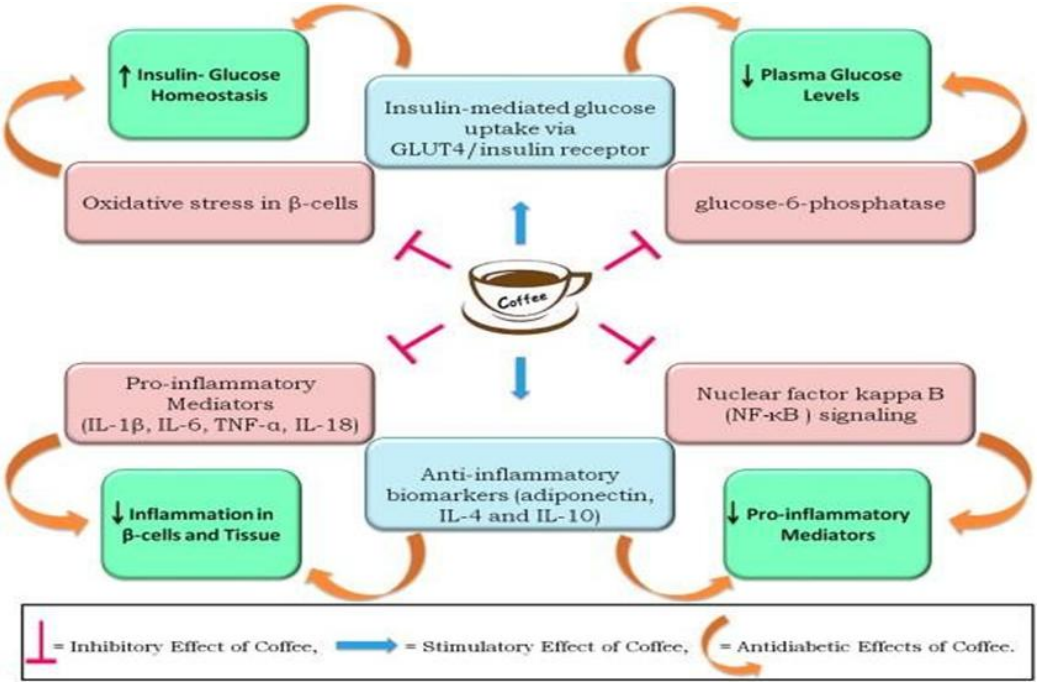

Fig. 1 Mechanism of Action of Caffeine

Mechanism of action metformin:

Patients with type 2 diabetes benefit from improved glucose tolerance due to the antihyperglycemic medication metformin, which lowers both basal and postprandial plasma glucose. Its pharmacologic modes of action differ from those of other oral antihyperglycemic drug classes. Metformin enhances insulin sensitivity by boosting peripheral glucose uptake and utilization while reducing intestinal glucose absorption and hepatic glucose synthesis. Metformin does not cause hyperinsulinemia or hypoglycemia, in contrast to sulfonylureas, in either type 2 diabetic patients or healthy individuals (with rare exceptions; see to PRECAUTIONS). Insulin production stays constant throughout metformin therapy, however fasting insulin levels and the daytime plasma insulin response may actually drop.

Foundamental Of Effervescents:

An alkali metal carbonate salt, frequently the API, and a soluble organic acid are the components of effervescence. If water comes into touch with this mixture, carbon dioxide is created.

Common instances of the alkalis and acids that are employed are as follows: Acids such as

- citric acid,
- Tartaric acid,
- Malic acid,
- Fumaric acid,
- adipic acid,
- sodium bicarbonate,
- carbonate of sodium,
- sesquicarbonate of sodium,
- bicarbonate of potassium,
- carbonate of potassium

Advantage of Effervascent Tablet:

- You don't have to swallow the tablet.
- Good intestinal and stomach tolerance.
- Increased mobility.
- Better palatability.
- Better stability.
- A more reliable reaction.
- Significant levels of active substances are included.
- Precise dosage.
- Enhanced Therapeutic Impact.
- Effervescent pills may be a viable option in isolated locations, particularly those where parenteral forms are unavailable because of exorbitant costs or a shortage of trained medical personnel.

Effervescent Tablets' Disadvantages:

- Some of the active substances have an unpleasant taste.
- Special packaging materials are needed for larger tablets.
- A significant number of more or less costly excipients and specialized production equipment make it rather costly to produce.
- Although a fine dispersion is now generally accepted, a clear solution is recommended for administration

METHODS AND MATERIALS:

Metformin HCl effervescent granule preparation:

The preparation of metformin effervescent granules involved a number of changes, including the use of an Ultrasonic Bath (Elmasonic E30H), the addition of PVP K-30, color, and flavor, as well as adjustments to the order and concentration of the excipients used, as detailed by Ashtosh, Rajesh, and Mukesh (Mohapatra et al., 2008). The materials indicated in Table 1 were used to make Metformin Effervescent Granules. Every component, including sodium bicarbonate, citric acid, tartaric acid, aspartame, erythritol, mannitol, metformin, and saccharin Na, was run through sieve number 40. Each formulation's required quantity is listed in Table 1, and all of the ingredients listed above were jointly crushed using a pestle and mortar. Granules were prepared using isopropyl alcohol and PVP K-30 as binder.Using an ultrasonic bath, PVP K-30 and both colors(Sunset Lake and Tartrazine Yellow) were dissolved in isopropyl alcohol in a 2:1 ratio. Both solutions were combined and used to soak the aforementioned dry mixture once the color and PVP K-30 had been thoroughly mixed. After passing through sieve number 60, the wet substance was dried in a Daihan Labtech Co. oven set to no more than 50˚C. The desiccated particles wereAfter passing through sieve number 40, the dried granules were combined with orange taste and p

Drug-excipient compatibility study:

The following excipients, which are utilized in the experiments, were examined for this study: These excipients were combined in various ratios based on the functional category. These combinations were maintained at 45°C S and 40°C + 75% RH.No.

Table 1-Category of Excipients

Sr. No.	Excipients	Category
1	Citric acid	Acidifying agent

2	Sodium citrate	Buffering agent
3	Tartaric acid	Acidifying agent
4	Sodium bicarbonate	Alkalizing agent
5	Sodium carbonate	Alkalizing agent
6	Ascorbic acid	Antioxidant
7	Polyethylene glycol-6000	Binding agent
8	Polyvinyl pyrollidone-30	Binding agent
9	Fumaric acid	Intermediate metabolite
10	Acidalant sodium benzoate	Lubricant
11	Sodium lauryl sulphate	Lubricant
12	Mannitol	Binding agent
13	Acesulfum potassium	Sweetner

Pre-compression study

Angle of repose (θ):

This is the greatest angle that can exist between a powder pile's surface and a horizontal plane. The angle of repose can be used to quantify the frictional force in loose powder or granules. It serves as an indicator of the powder's flow characteristics.49–50 tan θ = tan-1 (H/R) θ = H/R The angle of repose is denoted by θ. H is the pile's height. R is the pile's base radius. At a specific height (H), the powder combination was permitted to pass through the funnel that was fastened to a stand. The height and radius of the resulting powder pile were then measured in order to determine the angle of repose. The powder particles were carefully positioned to roll and slip over one another.

through the funnel's sidewalls. Angle of repose and powder flow characteristic are related.

Angle of repose as a measure of the characteristics of powder flow

Table 2: Angle of repose as a measure of the characteristics of powder flow

Repose angle (Degree)	Flow Type
<20	Excellent
20-30	Good
30-40	Acceptable
>40	Very good

Flow Rate:

The rate at which a specific mass emerges from a funnel with an appropriate diameter is known as the flow rate of a powder. Accurately weighed amounts of grains from each formulation were poured into a funnel with an 8 mm diameter opening to ascertain the flow rate. A timer was used to measure the amount of time needed for the entire granule mass to emerge from the aperture. The flow rate was determined using the following formula

$$\text{Flow rate} = \frac{\text{weight of granules}}{\text{Time in second}}$$

Bulk Density:

The mass of a powder was divided by the bulk volume in cm^3 to determine the bulk density. After passing through a conventional sieve number 20, the sample of roughly 50 cm3 of powder was carefully added to a 100 ml graduated cylinder. Three times, the cylinder was dropped from a height of one inch onto a hard wood surface at 2-second intervals. The final volume in cm3 of the sample contained in the cylinder was then divided by the sample weight in grams to determine the bulk density of each formulation. The following equation was used to calculate it:

Df = M/Vp where
Df = stands for bulk density.
M =is the sample weight in grams.
Vp = is the granules' ultimate volumes in cm3.

Tapped density:

The mass of a powder was divided by the tapped volume in centimeters to determine the tap ped density.

A 100 ml graduated cylinder is carefully filled with a sample of roughly 50 cm3 of powder th at has already been run through a standard sieve number 20.

The cylinder was dropped 100 times from a height of 1 inch onto a hard wood surface at 2- second intervals.

The final tapped volume in cm3 of the sample contained in the cylinder was then divided by the sample weight in grams to determine the tapped density of each formulation.

It was computed using the following equation:
Do = M/Vp where
Do= is the bulk density.
M= is the sample weight in grams.
Vp = granules' ultimate volumes in centimeter

Carr's Index:

Carr created an indirect technique for calculating powder flow from bulk densities. The proportion Potential powder arch or bridge strength and stability were directly correlated with a powder's compressibility. Each formulation's Carr's index was determined using the following equation
Where
Df= stands for bulk density, poured bulk, or fluff.
Do = Consolidated or Tapped Bulk Density.
Carr's Index as a powder flow indicator:

Table 3: Carr's Index as a powder flow indicator

Carr's index (%)	Flow type
15-15	Outstanding Flow type
12-16	Good
18-21	Passable to fair
23-35	Poor
33-38	Very low income
>40	Very impoverished

Evaluation of Effervasent Tablet:

Weight variation:

To ascertain whether several tablet batches are uniform, weight variation was calculated. 20 pills were weighed separately, the average weight was determined, and the weights of the individual tablets were compared to the average. If no more than two tablets deviate from the percentage restriction and no tablet differs by more than twice the percentage limit, the tablets pass the test. Table No. 6.18 displays the weight variation specification according to I.P. Limit of IP/BP USP 80 mg or less 10% of 130 mg or less Over
80 mg or Not more than 250 mg 7.5% Between 130 and 324 mg
250 mg or more 5% Over 324 mg

Tablet Thickness and Diameter:

For consistency in tablet size, tablet thickness and diameter were crucial. Vernier Calipers were used to measure diameter and thickness.

Tablet Hardness:

The hardness of a tablet determines how resistant it is to breakage or shipment under storage, transportation, and handling conditions prior to use. The Monsanto Hardness Tester was used to measure the hardness of each formulation's tablets. The hardness was expressed in kilograms per centimeter. The force needed to shatter a tablet under diametric compression is known as tablet crushing strength or hardness. For uncoated tablets, a hardness of roughly 3-5 kg/cm2 is

deemed adequate, and the force is expressed in kilograms.

Friability (F):

The Roche friabilator was used to determine the tablet's friability. This apparatus rotates a plastic chamber at 25 rpm, dropping a tablet six inches high with each rotation, subjecting it to the combined effects of shock and abrasion. A sample of tablets that had been previously weighed was put in the friabilator and rotated 100 times. The tablets were reweighed after being dusted with a gentle cotton towel. 0.5 to 1% is the USP limit. The formula provides the friability (F)

Effervescence time measurement:

One pill is put in a beaker with 200 milliliters of filtered water at 20 °C ± 1 °C. The effervescence period ends when a clear solution free of particles is achieved. For every formulation, the average of three measurements must be provided.

Effervescent solution determination

As soon as the dissolve time is over, a pH meter is used to measure the pH of the solution using one tablet in 200 milliliters of filtered water at 20 ± 1 °C. For every formulation, repeat the experiment three times.

CO2 content measurement:

Weight changes were calculated following the dissolution of one effervescent tablet in 100 milliliters of a 1N sulfuric acid solution. The amount of CO2 (mg) per tablet is displayed as the weight difference that was obtained. shows the three determinations' averages.

Evaluation of the water content:

For four hours, ten tablets of each formulation are dried in a desiccator filled with activated silica gel. It is okay to have 0.5% or less water.

Content Uniformity:

Ten tablets were chosen at random. After being moved into a 50 mL volumetric flask, each tablet was dissolved and diluted with 50 mL of phosphate buffer (pH 6.8). Phosphate buffer (pH 6.8) was used to dilute one milliliter of this solution to one hundred milliliters. UV spectroscopy at 246 nm was used to measure the amount of medication in each pill. IP is the standard limit for content uniformity:

USP: not more than 25 mg or 25%; BP: not more than 2 mg or 2%;

IP: active less than 10 mg or 10%.

Limit of 10 tabs NMT If two or three individual values are outside the range of 85 to 115%, then one-tab deviates from that range and none is outside of 75 to 125% of the average value/IP/BP/USP (Relative Standard Deviation less than or equal to 6%). Determine the moisture content balance Three desiccators are made with saturated salt solutions of potassium nitrate (to create 90% relative humidity at 18°C), sodium chloride (to create 71% relative humidity at 18°C), and sodium nitrite (to create 60% relative humidity at 18°C). Each formulation's three pills are put in desiccators. The Karl Fischer method and the autotitrator device are then used to calculate the equilibrium moisture content on the first day and seven days later.

Studies on Dissolution:

Using the USP Dissolution Testing Apparatus II (Paddle type), the rate at which atorvastatin was released from mouth-dissolving tablets was ascertained. Nine hundred milliliters of phosphate buffer with a pH of 6.8, kept at 37±0.50C, served as the dissolving media. For the duration of the investigation, the paddle speed was maintained at 50 rpm. Five milliliters of samples were taken out every five minutes, diluted to ten milliliters, and then replaniced with five milliliters of fresh dissolving media kept at the same temperature. The materials were subjected to spectrophotometric analysis at 246 nm with a blank of phosphate buffer pH 6.8. The volume of medicine released and the percentage of drug released at various time intervals were calculated by analyzing the raw dissolution data.

CONCLUSION:

The study investigated the significant correlation between compositions and test parameter results. When compared to regular tablets, effervescent pills improve the absorption of medications and have appealing aesthetic qualities. After a successful bioequivalence study to assess the efficacy of the prepared effervescent tablets, pharmaceutical companies worldwide can adopt this formulation, which will be a more appealing option for diabetic patients, particularly those receiving long-term anti-diabetic therapy. The study found that the most acceptable shelf life for metformin effervescent granules was 510 days at 4˚C and 425 days at room temperature. It also found that the granules were most stable when stored at 4˚C. Additionally, of the several Effervescent Granule formulations, the EG4 formulation has good flow properties with an angle of repose less than 30 and a quick disintegration in aqueous solution. Granules could therefore be an additional dosing form for antidiabetic medications.

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